HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

# UTILISATION OF INTERNAL AUDITS TO MONITOR AND GUIDE QUALITY SYSTEMS

*Master`s thesis*

Elina Krannila

Faculty of Pharmacy

Industrial Pharmacy

University of Helsinki

January 2012

HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

| Tiedekunta Fakultet Faculty | Laitos Institution Department | |
|---|---|---|
| Faculty of Pharmacy | Industrial Pharmacy | |
| Tekijä Författare Author | | |
| Elina Krannila | | |
| Työn nimi Arbetets titel Title | | |
| Utilisation of internal audits to monitor and guide quality systems | | |
| Oppiaine Läroämne Subject | | |
| Industrial pharmacy | | |
| Työn laji Arbetets art Level | Aika Datum Month and year | Sivumäärä Sidoantal Number of pages |
| Master's thesis | January 2012 | 144 + appendixes 4 |


Tiivistelmä Referat Abstract

In pharmaceutical industry GMP compliance and quality of operations can be ensured with quality management system (QMS). QMS is an operational system, which consist of multiple different elements depending on the size of the company and nature and complexity of its operations. For the QMS to be functional, documented and defined operations need to be managed and monitored systematically. Conducting internal audits has been considered necessary with regard to QMS, though it has not always been perceived as adding value or seen as an opportunity to utilise more fully. Internal audits are mainly utilized to control compliance to requirements. However, there are possibilities to utilise it more in improving and developing operations, preparation to external audits, quality risk assessment, finding out the best practices, basis for decision making, learning experience as well as the assessment of functionality and effectiveness of the QMS.

The aim of this study was to examine the utilisation of internal audits in Orion (Espoo) and find solutions to improve the utilisation of internal audits with QMS. The focus was on how internal audits can monitor and guide QMS and what is required from internal audits for monitoring and guidance of QMS. These aims were approached qualitatively by conducting semi-standardized open-ended interviews. Interviewees (n=9) were selected from both auditor and auditee side and they had their background in quality assurance or production. Data compiled from these interviews was analysed mainly by qualitative methods, using also some quantitative analysis.

Monitoring of the QMS can be looked at as the starting point to guide QMS. Valuable information can be gathered with internal audits with regard to QMS. By utilising this information, internal audit process and QMS can be improved and the quality of operations can be ensured. Based on this work internal audits can be utilised to monitor and have the potential to guide QMS under certain conditions. Internal audit topics need to be systematically selected, QMS needs to be monitored and guided based on the internal audit findings, flow and distribution of information needs to be efficient and flexible, and internal audits should be better utilised and managed. Further research is needed on the development and deployment of tools to aid better utilisation of internal audits in the control of QMS. Also ways to measure the effects of internal auditing should be further investigated.



Avainsanat – Nyckelord – Keywords

quality, quality system, quality management system, internal audit, qualitative research, interview

Säilytyspaikka – Förvaringställe – Where deposited

Orion Corporation/ Division of Pharmaceutical Technology

Muita tietoja – Övriga uppgifter – Additional information

Supervisors: Professor Anne Juppo (University of Helsinki) and Ph.D. (Pharm.) Marja Salo (Orion)

HELSINGIN YLIOPISTO
HELSINGFORS UNIVERSITET
UNIVERSITY OF HELSINKI

| Tiedekunta Fakultet Faculty | Laitos Institution Department | |
|---|---|---|
| Farmasian tiedekunta | Teollisuusfarmasia | |
| Tekijä Författare Author | | |
| Elina Krannila | | |
| Työn nimi Arbetets titel Title | | |
| Sisäisten auditointien hyödyntäminen laatujärjestelmän tarkkailussa ja ohjailussa | | |
| Oppiaine Läroämne Subject | | |
| Teollisuusfarmasia | | |
| Työn laji Arbetets art Level | Aika Datum Month and year | Sivumäärä Sidoantal Number of pages |
| pro gradu | Tammikuu 2012 | 144 + liitteet 4 |


Tiivistelmä Referat Abstract

Lääketeollisuudessa laadukas ja GMP:n mukainen toiminta pyritään turvaamaan laadunhallintajärjestelmän (LHJ:n) avulla. LHJ on toimintajärjestelmä, joka koostuu useasta eri tekijästä yrityksen koosta, toiminnoista ja niiden monimutkaisuudesta riippuen. Edellytyksenä järjestelmän toimivuudelle ovat määritellyt ja dokumentoidut toiminnot, joita hallinnoidaan ja monitoroidaan järjestelmällisesti. Sisäinen tarkastus on välttämätön toiminto LHJ:ssä, mutta sen tuomaa lisäarvoa ja hyödyntämismahdollisuuksia ei ole aina nähty. Sisäisiä tarkastuksia hyödynnetään pääasiassa vaatimusten mukaisuuden tarkastelussa. Mahdollisuuksia olisi kuitenkin hyödyntää sitä enemmän myös toiminnan parantamisessa ja kehityksessä, ulkoiseen tarkastukseen valmistautumisessa, riskien kartoittamisessa, hyvien toimintatapojen levittämisessä, päätöksen teon perustana, oppimistilanteena sekä laatujärjestelmän toimivuuden ja tehokkuuden arvioinnissa.

Tämän tutkimuksen tavoitteena oli tutkia sisäisten tarkastuksien hyödyntämistä Orionilla (Espoo) ja löytää ratkaisuja sisäisten tarkastuksien hyödyntämiseen LHJ:n kanssa. Painopisteenä oli, miten sisäisillä tarkastuksilla voidaan tarkastella ja ohjata LHJ:ä ja mitä sisäisiltä tarkastuksilta edellytetään, jotta tämä toteutuisi. Näitä tutkimustavoitteita lähestyttiin laadullisesti puoli standardoidun, avoimia kysymyksiä sisältävien haastatteluiden muodossa. Haastateltavien joukkoon (n=9) valittiin sekä tarkastajia että tarkastettavia, joilla oli tausta laadunvarmistuksesta tai tuotannosta. Haastattelun sisältö analysoitiin pääasiassa laadullisin menetelmin, käyttäen apuna myös määrällistä analyysiä

LHJ:n tarkastelua voidaan pitää lähtökohtana sen ohjaamiselle. Sisäisten tarkastuksien avulla voidaan kerätä arvokasta tietoa LHJ:stä. Hyödyntämällä tätä tietoa, sisäistä tarkastusta ja LHJ:ä voidaan parantaa ja näin toiminnan laatu voidaan turvata. Tämän työn perusteella sisäisillä tarkastuksilla voidaan tarkastella ja on mahdollista ohjata LHJ:ä tietyin edellytyksin. Tarkastusaiheet tulee valita järjestelmällisesti, laatujärjestelmää tulee tarkkailla ja ohjata nimenomaan sisäisten tarkastuksien havaintojen avulla, tiedonkulun ja levityksen tulee olla tehokasta ja joustavaa ja sisäisiä tarkastuksia tulee hyödyntää ja hallinnoida paremmin. Lisätutkimuksia tarvitaan, jotta voitaisiin kehittää ja ottaa käyttöön työkaluja, jotka tukevat sisäisten tarkastuksien käyttöä LHJ:n hallinnassa. Myös tapoja mitata sisäisten tarkastuksien vaikutuksia tulisi tutkia.



Avainsanat – Nyckelord – Keywords

laatu, laatujärjestelmä, laadunhallintajärjestelmä, sisäinen tarkastus, laadullinen tutkimus, haastattelu

Säilytyspaikka – Förvaringställe – Where deposited

Orion Oyj./ Farmasian teknologian osasto

Muita tietoja – Övriga uppgifter – Additional information

Ohjaajat: Professori Anne Juppo (Helsingin Yliopisto) ja FaT Marja Salo (Orion)

ABBREVIATIONS

Corrective and preventive action (CAPA)
Critical Process Parameters (CPP)
Critical Quality Attributes (CQA)
European Medicines Agency (EMA)
European foundation for quality management (EFQM)
Failure Mode, Effects and Criticality Analysis (FMECA)
Failure Mode Effects Analysis (FMEA)
Fault Tree Analysis (FTA)
Finnish Medicines Agency (FIMEA)
Food and Drug Administration (FDA)
Good manufacturing practice (GMP)
Hazard analysis and critical control points (HAACCP)
Hazard operability analysis (HAZOP)
International Conference on harmonization (ICH)
International standardization organization (ISO)
Plan-Do-Study-Act (PDSA)
Plan-Do-Check-Act (PDCA)
Preliminary hazard analysis (PHA)
Quality assurance (QA)
Quality by design (QbD)
Quality Control (QC)
Quality system (QS)
Quality management system (QMS)
Quality target product profile (QTPP)
Qualified Person (QP)
Standard Operation Procedure (SOP)
Total quality management (TQM)

LIST OF APPENDIXES

TABLE OF CONTENTS

# 1 INTRODUCTION

In today's global market it is important for companies to sustain and improve both the performance and quality of products and processes and adapt quickly to changes in order to be competitive. Pharmaceutical industry is no exception. The discovery of a new chemical entity and the development of a drug product are both time consuming and costly (DiMasi et al. 2002). Rising cost of the development and marketing of the products together with the need to get these products to market more quickly are key drivers in the pharmaceutical industry (McAdam and Baron 2002).

Quality of a product is usually defined by the customer (Juran 1992). Pharmaceutical products are exception to this since a third party is defining the quality. The heavy regulation in pharmaceutical industry is due to the safety issues regarding the use of medicines (McAdam and Barron 2002).

Because of high demands on quality, safety and the cost of the product, all processes should be monitored and improved in a timely manner. Quality management system (QMS) is built to ensure the quality of the drug product. Internal auditing can be seen as an important part of QMS as it is one of the tools used to monitor quality, performance and compliance to set standards (Skubch and Zimmer 2009).

Internal auditing can be followed through at different levels as the quality system and the separate processes or parts of the processes can be internally audited (Pharmaceutical quality group 2001). This approach ensures the safety and quality of the product and helps to maintain effective processes more fully.

Internal audits in pharmaceutical industry, regarding both quality systems and other processes, can be seen as having two main functions: firstly to ensure compliance with good manufacturing practice (GMP) and secondly to continually improve the quality QMS and processes (Jeronic 2010). Conducting internal audits is considered as a GMP-requirement to objectively evaluate company's own functions and also as a learning

experience as it deepens knowledge about own system and processes (GMP Ch 9, WHO Annex 4).

A lot of the articles concerning internal audits are from the field of accounting. This was mostly disregarded in this work, due to dissimilarities of the fields. Other industry (e.g. nuclear, automotive, aerospace and food industry), which are similar to pharmaceutical industry in nature (regulative control and safety aspects), use also audits to assure their quality and as part of their QMSs. Many of the articles covered mostly the auditing of subcontractors or implementation of a QMS than internal audits discussed in this work (Goodwin 2002, Beckmerhagen et al. 2003).

Former work in this field has mostly been done on the process of internal audit itself (e.g. Karapetrovic and Wilborne 2000 and 2001, Beckmerhagen et al. 2004, Elliot et al. 2007) and on internal audit as a mean to gain compliance and to continuously improve systems (Beecroft 1996, Kaye and Anderson 1999). Audits have been studied both from the auditor and auditee point of view. These studies have mainly been survey studies (Elliot et al. 2007, Jeronic 2010) or case studies of a specific way of working in a particular company (Beckmerhagen et al 2003, Kausek 2008, Morris 2008).

This work introduces how internal audits could be more fully utilised in pharmaceutical industry and what other benefits besides compliance and improvements internal audits might have. There is (to my knowledge) no research done specifically on the utilisation of internal audits in pharmaceutical field in an extensive way. In this work the research problems were approached qualitatively, by using interviews as a way to gather information from one case company and content analysis to analyse and interpret the data. This way a deeper understanding of the internal audit processes was reached.

The aim of this study is to review the status of internal audits and to find solutions to improve the utilisation of internal audits with quality systems at one case company at one site, namely Orion Espoo. The focus will be on how internal audits can monitor and guide quality systems.

# 2 QUALITY

Quality is very closely linked to the context in which it is used. Thus it is difficult to give a simple definition for quality. As stated by Garvin “quality is not a single, recognizable characteristic; rather it is multifaceted and appears in many different forms” (1984). Besides the definitions, quality also has multiple dimensions. Garvin has listed eight dimensions of product quality: performance, features, reliability, conformance, durability, serviceability, aesthetics and perceived quality. These dimensions imply that quality should be evaluated and improved at different dimension (Forker et al 1996).

A definition of quality depends on the viewpoint and the circumstances where it is applied. There exist five universally known approaches to quality: transcendent, user-based, manufacturing-based, product-based and value-based (Garvin 1988). Each approach looks at quality from a specific perspective and takes into consideration the different dimensions of quality. Next, each approach will be looked at more closely and linked together with quality in pharmaceutical industry.

## 2.1 Transcendent approach to quality

Transcendent quality can be described as indefinable excellence, which can only be recognised through experience (Pirsing 1992). This is the intangible and abstract part of quality, which often makes the quality so hard to define regardless of the field of business.

## 2.2 User-based approach to quality

Juran describes quality as “fitness for use“ (Juran 1992). This can be considered as a user-based approach as it takes in to account the customer point of view. It considers whether a product meets the expectations of the customer or not. Ishikawa (1976) brings in the product development view to this approach, when he points out that a good product can only be produced when customer needs are taken into consideration.

Customer oriented approach in defining quality is widely used in the service sector where empirical studies have been conducted to find out how customers judge quality and whether the services meet or exceed their expectations (Zeithaml 1990). The user-based approach to quality can be applied also in the manufacturing industry. A survey study by Sebastianelli and Tamimi (2002) revealed that the user-based definition for quality was actually the most popularly used in manufacturing companies in USA. In their research the user-based definition for product quality was significantly linked with aesthetics and perceived quality of the product.

It is hard for the consumer though, to estimate and perceive the quality of a medicinal product. Medicinal products are often indirectly chosen. They can be prescribed by doctors, recommended by pharmacists, and/or covered by health insurance. This is why a third party defines quality in pharmaceutical field, namely the regulatory authorities. There exists very low tolerance for any deviations and variations for the quality of pharmaceutical products due to critical consequences of mistakes (Adis 2008). Quality of a pharmaceutical product is closely linked to safety and efficacy of the product (Sharp 2000). Guidelines such as Good Manufacturing Practice (GMP) set by regulatory authorities dictate the standard for quality in pharmaceutical industry for both products and systems (GMP Chapter 1).

## 2.3 Manufacture-based approach to quality

Quality has been traditionally described from the manufacturing point of view as conformance to requirements or specifications (Crosby 1979, Garvin 1984). Also International Standardisation Organization (ISO) and International Conference on Harmonisation (ICH) have a similar definition for quality. (ICH is partially based on ISO standards.) Quality is defined by ISO as “a degree to which a set of inherent characteristics or properties of a product system or process fulfils the set requirements” (ICH Q9, SFS- EN ISO 9000:2005).

Perhaps the manufacture-based definition suits the pharmaceutical product and processes best, as both the product and the processes are monitored to ensure

compliance with set (quality) standards. Measurements of the systems need to fulfil the expectance criteria set up for the different processes to produce a quality product (Feldman 2005, ICH Q8).

Quality of drug products can be defined from the regulatory point of view as a product which "delivers clinical performance per label claims" (Woodcock 2004). This means that the product itself, and all the related actions, which contribute to the development and production of the product, e.g. clinical tests, analysis, production and all the documentation, has to comply with its marketing authorisation.

## 2.4 Product-based approach to quality

A product having good features and being free from deficiencies is considered a quality product (Juran 1992). Product characteristics and its features and attributes are measurable and these can be monitored and improved upon (Garvin 1984). This way measurements of product characteristics can give an objective idea of the product quality.

Product and process understanding is emphasized, as pharmaceutical products are becoming more and more complex (Ricci and Fraser 2006). Development and manufacture of pharmaceutical products needs to be predictable and the aim is to produce a quality product consistently over time. The concept of quality by design is linked to product-based approach on quality and has an established position in pharmaceutical industry (more about this concept in the next chapter).

## 2.5 Value-based approach to quality

Value-based approach takes into consideration that quality should be achieved at accepted cost. Loss avoidance means avoiding the costs caused by defect products (Ricci and Fraser 2006, Taguchi and Clausing 1990). If a product is defect, it creates costs because the product and the manufacturing process have to be repaired and the product cannot be sold. Quality losses in factories can be measured as a value of these

costs and losses. Process failures have to be reduced in order to gain a more robust and valuable quality product.

Quality related problems and costs in the pharmaceutical industry can be avoided with better process understanding. Also a greater production effectiveness can be achieved when processes are fully understood and this in turn may "accelerate time to peak sales by as much as two years" (Figure 1). Besides, if a pharmaceutical company can demonstrate that they have a deep understanding of their product and process it can form a basis for a more flexible regulatory approach (ICH Q8, Jeronic 2010).

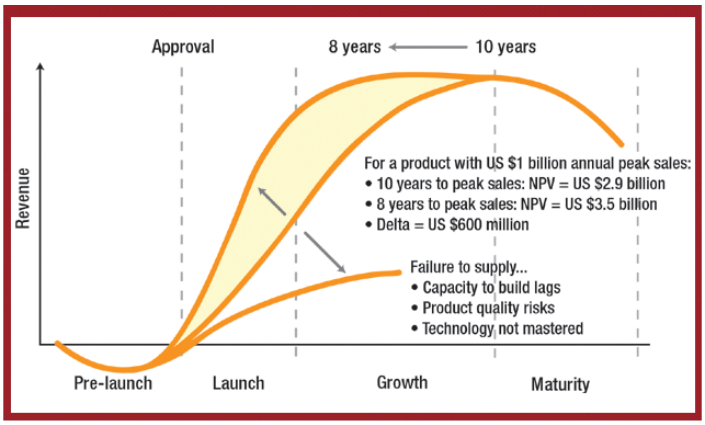


Figure 1. Better process understanding can lead to added value of sales (Ricci and Fraser 2006).

# 3 QUALITY MANAGEMENT

The different approaches and dimensions of quality make the management of quality challenging. This gives a good reason to take a systematic and comprehensive approach to quality. In this chapter philosophies of quality management are discussed and methods to manage quality are described.

To achieve quality, quality has to be managed. Juran uses a universal approach to describe quality management (Juran 1986). This approach is the famous Juran Trilogy where three basic quality processes: planning, control and improvement are combined and utilised together to manage quality. Juran emphasizes the importance of uniformity of actions to be able to achieve a common quality goal and to manage quality towards a desired direction. This quality management concept can be applied to management systems and manufacturing processes.

## 3.1 Quality planning

In this part, quality planning at corporate and manufacture level are discussed and they are linked to quality planning in pharmaceutical industry. Also the role of management is considered.

### 3.1.1 Quality planning at corporate level

Quality managing starts with thorough quality planning where quality objectives and the methods to realise them are set (ICH Q 10, Juran 1986). Quality policy, determined by the senior management of the company, expresses the company`s view on quality-related matters and indicates the intensions and directions with these matters in a general level. Quality objectives describe in a more detailed way the spesific quality goals and the attainment of them. The infrastructure and necessary resources have to be in place in order to achieve these quality objectives. This enables the company to carry out its processes according to quality plans and to meet the set quality standards and requirements. According to EU GMP the quality objective for a pharmaceutical manufacturing company should be to ‘‘ensure that [the products] are fit for their

intended use, comply with the requirements of the Marketing Authorisation and do not place patients at risk due to inadequate safety, quality or efficacy" (EU GMP Chapter 1). Therefore, to attain the quality objectives in pharmaceutical manufacturing environment, efforts to ensure and manage quality has to also consider safety and efficacy aspects.

The realisation of quality objectives is the responsibility of the senior management and requires tight collaboration inside the organization. A QMS can help to comprehensively involve different parties towards realising common quality goals and to gather scattered functions together more systematically. QMS is well documented in the quality manual together with the quality policy, description of pharmaceutical processes and management responsibilities and this system should also be monitored for its effectiveness (GMP chapter 1, ICH Q10). Quality policy and quality objectives should be occasionally subjected to revision to keep up with the constantly changing and evolving environment and regulations. The quality planning activities and their relations are shown in Figure 2.


Figure 2. Quality planning (adapted from ICH Q10 and Juran 1986).

### 3.1.2 Quality planning in the manufacturing environment

Quality planning is also important in the manufacturing level. Quality should be planned and built in to the system by design, not by testing it in to products (ICH Q 8, Juran 1992, Yu 2008). This is a systematic concept, which Juran describes as quality by design (QbD) and is widely used in pharmaceutical industry. The key element is to understand the impact of variations and sources of these variations to the designed system. QbD can deepen process understanding and help finding opportunities for improvements with the process performance (Snee 2009). It can also help to maintain the process under control. Altogether QbD reduces risks involved with the production and can eliminate future problems.

The quality parameters for the product are defined in quality target product profile (QTPP), which contains all the important product details relating to quality, safety and efficacy of the product (McConnel et al 2010, ICH Q8, Juran 1992). With the help of QTPP, the product is developed with specified goals and is "planned with the end in mind" (Yu 2008). Those properties, which have impact on the product quality are defined as critical quality attributes (CQA). Critical process parameters are considered when selecting the manufacturing process because they have a direct influence on CQA.

A drug product should be designed with the patient needs in mind (Feldman 2005, ICH Q8). Tests should be planned and done to monitor quality and to find any deviations, which could affect the quality of the product. There should exist a wholesome approach to deal with quality-related issues in the manufacturing environment (ICH Q10). QMS can be developed and maintained to ensure the desired quality of the product at all times. Quality cannot be tested into the product. It should be built into pharmaceutical manufacturing process by establishing specification limits and manufacturing controls in forehand e.g. with the help of QbD or design space (McConnel et al 2010, ICH Q8).

### 3.1.3 Role of management in managing quality

Quality is made and developed by the management of the company (Deming 1994). Leadership is needed in order to keep the entire company focused on quality related issues. This is achieved through establishing quality policy and objectives, which is the responsibility of the senior management (GMP Chapter 1, Juran 1986). It is not enough to set the standards, management also has to monitor the achievement of these objectives (ICH Q10). This happens through management review (more about management review in section 6.3.4), where information is gathered about quality functions and brought to management`s attention. After this it is, again, senior managements responsibility to adjust company`s function or quality policy according to the information gained about own systems.

Garvin (1983) has studied failure rates in manufacturing environment (production of air conditioners) by measuring both internally and externally observed defects. He concluded that those companies with better quality performance (less defects) managed quality by having the managements support on quality-related issues, setting goals for quality and by giving feedback information of quality data back to managers. This way management has an active role and knows what is going on. Management is then able to redirect resources and attention to possible problem areas and improve quality performance. In my opinion, decision makers (management/managers) are at the core when it comes to managing quality. They need to decide, how to measure quality and react to quality related issues. In this way they have a significant influence on managing quality effectively as they rely on the latest information about their own processes.

## 3.2 Quality control and Quality assurance

When the process or system is operational, quality control ensures that it runs effectively and according to plans (Juran 1986). Quality control can help detect problems, which can be solved by statistically analysing the collected quality data and figuring the relation between the cause and effect (Ishikawa 1976). In the manufacturing environment causes of variation are determined and corrective actions are taken in order

to keep the process under control. Design space is an operational area utilised in pharmaceutical industry, where the process performance is kept under control even when small changes are made (ICH Q8 2009). It is applied together with QbD to provide assurance of quality. The main benefit of these two approaches is that changes can be managed in a controlled way by understanding their inputs.

Quality control exists in different levels according to what is being controlled. QMSs can be controlled with quality system audits to ensure that QMS functions effectively and according to plans. In the pharmaceutical industry findings from internal audits and the handling of complaints and deviations can also indicate some trends regarding the quality of the product (EU GMP Chapter 8 and 9).

### 3.2.1 Monitoring and measuring quality

Process performance should be systematically measured and monitored to gain information on current status of the performance and ensure continuous improvement of the process (Kueng 2000). With the help of process performance measurement the realization of business goals can be monitored and the organizational goals become evident throughout the organization. Monitoring and measuring of performance can also be used to gain information about the functionality of the supply chain (Beamon 1999) and quality management (Saraph et al. 1989). Together these performance measurements can give comprehensive information on the existing quality or performance status of the functions in the organization as they drill deep and reach different layers of the operations (Figure 3). Some of the measurements give detailed information and others can view the overall performance.

There exist different approaches to measure and to monitor performance and to find areas for improvement. These approaches differ from one another by having different focus or measuring qualitative or quantitative aspects of performance (Kaye and Anderson 1998, Kueng 2000). Examples of ways to measure performance are: balanced score card, self assessment (EFQM), statistical process control, customer complaints, auditing and internal auditing.

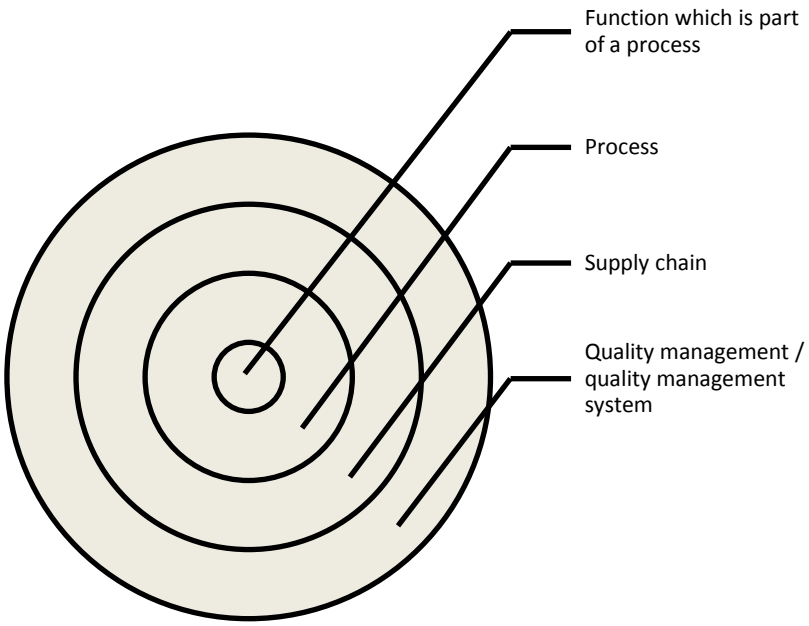


Figure 3. Objects of monitoring and measurement.

Saraph et al. (1989) have identified eight critical factors (Table 1) for identification of areas for improvement in quality management. These factors take into consideration different aspects of effective quality management and are based on organizational requirements for quality management found in literature. As can be seen in Table 1, a lot of factors need to be considered as quality management is comprehensively evaluated. These factors range from management level to employee level and include different aspects in manufacturing environment and the supply chain, such as the quality assurance (quality department), development (product design), production, suppliers etc.

Data is collected by measuring indicators of performance, which are chosen according to goals of the process (the specific functions of the process) and business goals derived from top management and business objectives (Kueng 2000). The choice of measurement indicators is also affected by new technology being developed (e.g. analysing instruments) and changes in regulations or procedures. It is important to choose what to measure as this contributes to the information being formed and decisions made based on this information.

Table 1. Critical factors of quality management (Adapted from Saraph et al. 1989).

| **Critical factors** | | **Explanation** |
|---|---|---|
| 1 | The role of quality management and quality policy | Quality planning, setting quality goals, being involved in quality improvements. |
| 2 | Role of the quality department | Consultative, effective, having access to top management. |
| 3 | Training | Quality-related training |
| 4 | Product design | Producibility, setting clarifying specifications and procedures. |
| 5 | Supplier quality management | Suppliers should be selected based on quality, education of supplier, assurance of the product quality from the purchasing and supplier side. |
| 6 | Process management | Less inspection, more employee self-inspection. Preventative maintenance. |
| 7 | Quality data and reporting | Feedback of quality data for employees and managers for problem solving. |
| 8 | Employee relations | Quality awareness and responsibility for all employees. Feedback to employees on their quality performance. |

As the data is being analyzed it should be compared with previous data and target values. Cause and effect diagrams and trend and gap analysis can be made to better illustrate the information. To gain the full benefit of measuring and analyzing data, the collected data needs to be managed properly. The information gained should be distributed in the organization to both top management and the people involved with the process being monitored.

The measurement and assessment of the process can be seen as a three-tier process (Figure 4). At the core is the process itself (worker). In the second level the process is monitored, measured and improved and in the third level definition of goals, indicators for measurement and target values are made (management).

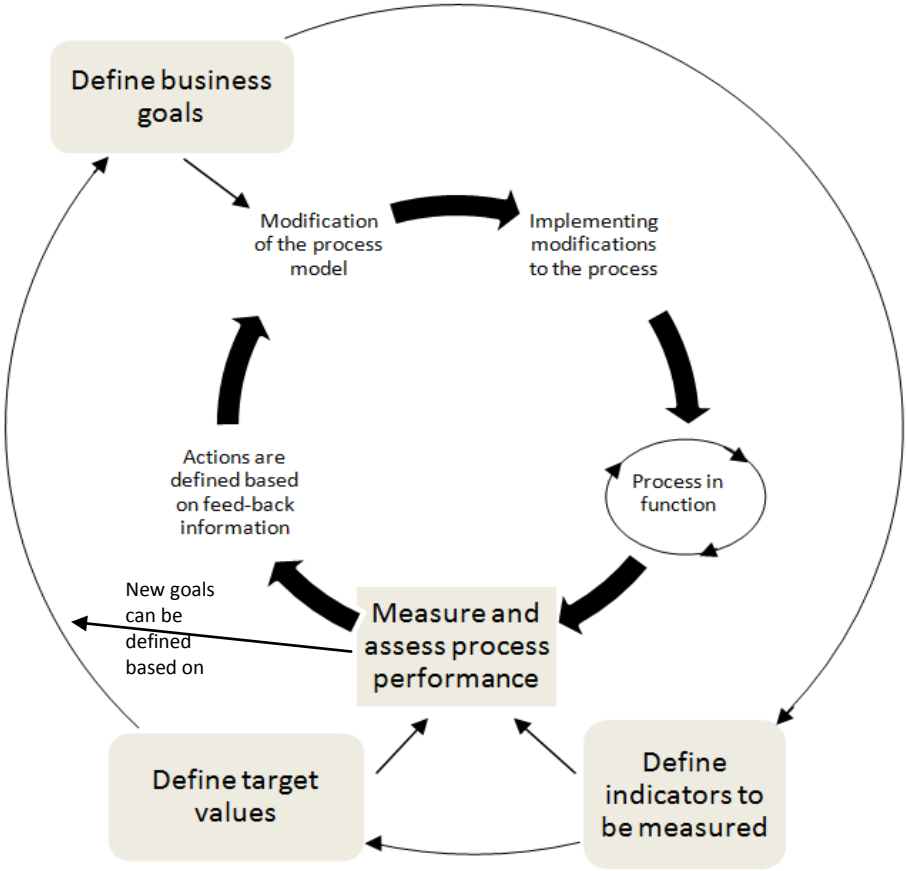


Figure 4. “Process management circle” (Adapted from Kueng 2000).

## 3.3 Quality improvements

There exists many quality improvement theories and their goal is to enhance operational and financial performance quality (Adam 1994). Upper management needs to provide enough resources to promote improvement (Juran 1986). Continual evaluation of quality (e.g. in the form of auditing) can identify places where improvements are needed by comparing performance against set quality goals. When the needs are established and management gets involved, by providing resources and financial support, necessary changes can be made and the quality of the process can be improved. In order to improve processes in the long run, quality has to be continously monitored and evaluated, and necassary action needs to be taken.

### 3.3.1 Improving the quality of processes and quality management

By improving quality in the operational level, productivity can be improved due to less rework as defects are avoided (Deming 1982). Also quality management can be improved. This benefit can be gained by utilising the elements of quality management techniques or by establishing QMS (e.g. TQM and ISO 9000) (Lee et al. 1999).

Aravindan et al. have studied how manufacturing companies utilize systematic and strategic quality management aspects to improve quality (1996). They recognized eight vital quality strategies, which were needed to reach quality enhancement (Figure 6). All the manufacturing companies (n=152) used employee involvement programs to gain better use of human knowledge and about one third (n=54) of the companies managed quality systems continuously. All the other aspects such as quality information management and reacting to quality audit reports were mostly overlooked. This might be the reason why companies found it difficult to execute breakthroughs with quality improvements. This shows that concentrating on only few aspects of the quality strategies does not contribute to total quality management (TQM) (more about this concept in the next chapter) nor to quality enhancements.

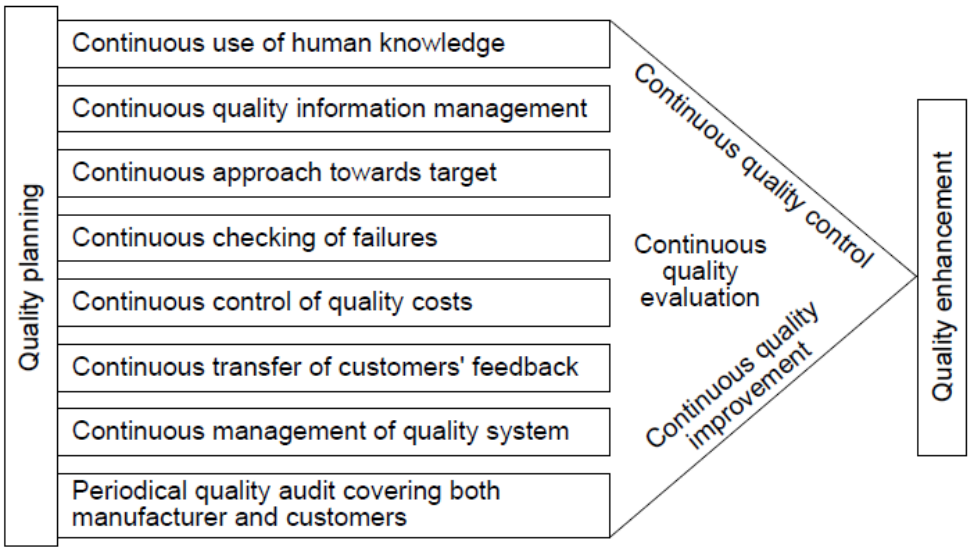


Figure 6. Different strategic quality aspects contribute to quality enhancement (Aravindan et al. 1996).

### 3.3.2 Plan-Do-Study-Act

According to Deming the Plan-Do-Study-Act (PDSA) cycle can detect the places for and effects of improvements (Figure 5, 1982). This can further promote improvement and understanding of the process. The cycle captures the whole idea of quality management. To start with, actions need to be well planned and carried out. After this, variation in the process should be observed and the reason (root cause) for this variation should be studied. The last stage is the improvement stage where the system should be adjusted based on the observed and studied results. This could mean corrective actions or improvements to the system. As knowledge about the system is accumulating through the cycle and different actions are taken, the process is improved. This improvement happens by feeding all the gathered information back into planning of actions. The knowledge also helps to predict what might be demanded of processes and systems in the future.

A different version of this cycle, a Plan-Do-Check-Act (PDCA) cycle is used in many companies to manage processes but it is often not successfully utilised to promote improvement (Gupta 2006). PDSA emphasizes the knowledge for finding the reason for variation and PDCA concentrates on being inside certain specification limits. The latter approach has a more limited chance to promote improvement, because it only implies that the product or process has to be inside certain limits and does not give underlying reason or goal for improvement. Gupta suggests a 4 P`s (Prepare-Perform-Perfect-Progress) cycle for process management (Figure 5). It takes into consideration the preparation phase where information, tools, approaches and skills are identified and applied to turn inputs to outputs at the “perform”-phase. This preparation phase is important as “most root-cause analysis leads to one of the preparation items as a source of problem”. In-process controls are carefully chosen and evaluation on whether the product or process is perfect (on target) is done. Progress does not concentrate on corrective actions only, but drives improvement.

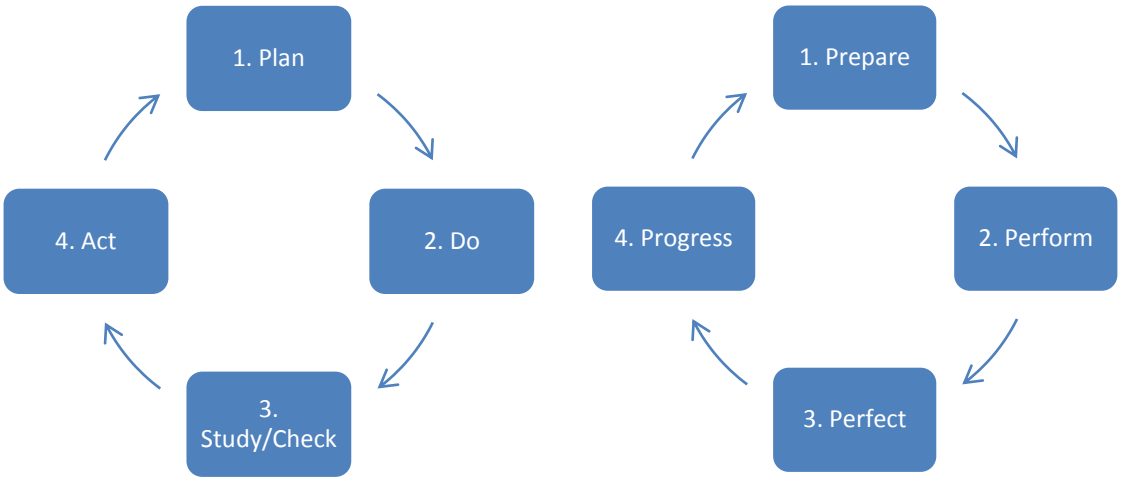


Figure 5. PDSA/PDCA-cycle and 4 P`s of process management (Adapted from Deming 1982, Gupta 2006).

# 4 QUALITY MANAGEMENT SYSTEMS

In this chapter we shall look at different types of approaches to QMSs. Questions like how QMSs work and can be implemented and why QMSs are needed in pharmaceutical industry are answered.

## 4.1 Definition of quality management system

QMS is an operational system consisting of several different elements to achieve a better overall management of quality (Ricci and Fraser 2006, Juran 1992, SFS-EN ISO 9000:2005). It is not a readymade or fixed system, which can be applied as it is. Rather it is build up systematically and improved over time and tailored after company`s own goals, needs and operations. QMS requires commitment from management, as it is applied to establish and maintain a quality policy and to direct the organization towards achieving its quality objectives. QMS also controls and improves the organization with regard to quality and compliance.

QMS can be thought as a process-based system where a network of interrelated processes manages quality and helps to realise quality management (SFS-EN ISO 9000:2005). ICH`s definition, based on ISO 9000, states that a pharmaceutical quality system "[directs] and [controls] a pharmaceutical company with regard to quality" (ICH Q10). Both the process-based model for QMS and pharmaceutical quality system are described in more detail later in this chapter.

## 4.2 Background for quality management systems

Different types of management systems exist and are build-up based on, which part of business one wants to manage. Financial, safety and environmental management systems are present alongside QMS and can sometimes be integrated to form one management system to manage business more thoroughly (Jonker and Karapetrovic 2004, Karapetrovic 2002).

The model for quality management has evolved in the last decades (Figure 7) (Edwards 2008). It has shifted from product-oriented quality control via quality assurance of the process to a more extensive quality-system approach.

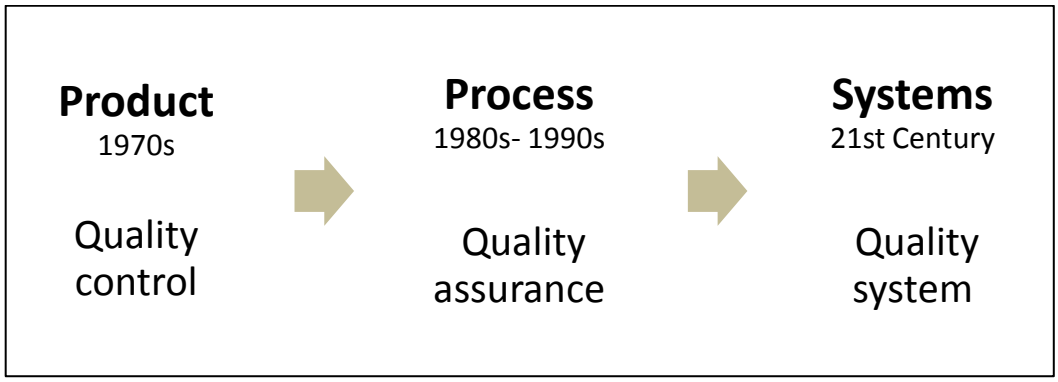


Figure 7. "Models of quality" (Edwards 2008).

A quality management team can be formed to develop a quality plan and to establish and maintain the QMS (Harbour and Kieffer 2000). A compliance master plan can also guide with the implementation of the QMS (Borkar 2006). The reason behind implementing a QMS is to control and improve current processes and system (Edwards 2008). A QMS ensures that guidelines are being followed and reports whenever deviations from standards occurs (Adis 2008). A good system captures variance in a process or a system and is able to manage the whole flow of the process. This includes problem solving and reporting problems forward to improve the process.

Having a poor QMS can lead to non-conformance and cause recalls (Edwards 2008, Markovitz 2010). The cost of poor quality in the form of recalls is expensive for any company, and it can mean loss of income and reputation. These costs should be avoided by utilising QMS, which is implemented throughout the product`s lifecycle. If the quality is compromised by taking shortcuts, avoiding costs or implementing quick fix on a problem without considering the real cause of the problem or the long-term effects, the company can get in to trouble and have increased costs.

## 4.3 Different types of quality management systems

There exist similar goals for QMSs, but the ways to achieve these goals differ (Andersson et al. 2006). The function of QMS may overlap with another and a company`s QMS is often built up by using different elements of the systems simultaneously regardless of the field of business (Antony and Banuelas 2002). Figure 8 shows the portions of different QMS used in manufacturing and service organisations in UK. Very few companies utilised only one QMS (3-6%). Most of the companies either had a combination of ISO-9000 and TQM (40%) or ISO-9000, TQM and Six Sigma (31%). Some of the organisations (14%) had not yet reached a systematic quality level with the help of a QMS.

One type of QMS is often not enough to reach complete quality management. For instance, ISO 9000 certification alone does not necessary contribute to improved business performance (Terziovski and Samson 1997). Wide range of elements of quality management (e.g. TQM) has to be already established to gain the full benefits of ISO 9000 certification. Other QMS, such as Lean and Six Sigma can also be integrated to form a more complete QMS with fewer limitations (Arnheiter and Maleyeff 2005). In Table 2, information has been gathered to sum up the different approaches to manage quality.

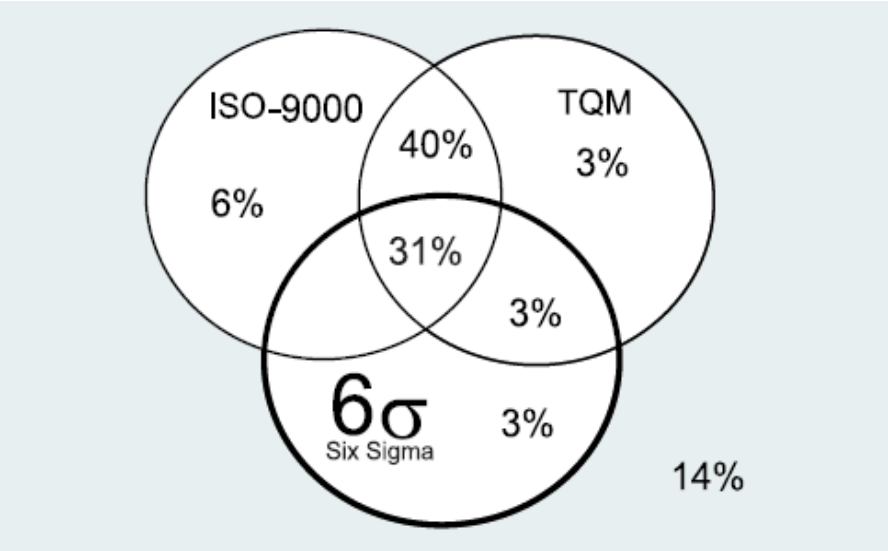


Figure 8. Percentages of implemented QMS (Antony and Banuelas 2002)

Table 2. Comparison of the different QMS (Andersson et al. 2006, Antony and Coronado 2002, Arnheiter and Maleyeff 2005, Bou-Llusar et al. 2005, Drakulich 2008, EN ISO 9000:2005, Lau and Anderson 1998).

| | **TQM** | **Lean** | **Six Sigma** | **EFQM** | **ISO 9000** | **ICH Q10** |
|---|---|---|---|---|---|---|
| **Goal** | Total quality management by focusing on customers | Reduce waste and variability | Defects occur at the rate of 3.4 defects per million opportunities | Improved business excellence | Improved business performance and getting a certified quality system, continuous improvement | Establish a state of control, help to achieve product realisation and to facilitate continual improvement |
| **Method** | Everyone is involved in managing quality and improving processes | Continuous improvement by streamlining the flow of production | Eliminate defects by reducing variation | Self-assessment, current status is compared with the EFQM framework | Process-based approach where inputs are turned into outputs with the help of company`s resources | Monitor performance, implement CAPA and change and establish feedback system (management review) |
| **Focus** | Customer | Customer | Internal customer | Customer | Customer | Safety |
| **Scale** | Company-wide | Supply chain/ company-wide | Process, project | Company-wide | Company-wide | manufacturing environment/ company-wide |
| **Important factors** | Top-management involvement, PDSA-cycle | Just-in-time production, outsourcing, | Statistical and problem-solving tools | Leadership | Customer focus | Management responsibility, Knowledge and risk management |
| **Limitations** | May be too general and unclear | Not flexible enough | Concentrates on one problem at a time, No system view. | Complicated model with complex scoring mechanism if cause-effect relationship not established | Certification must not be the only driving force. | Quit general in nature. Only a recommendation. Does not have the customer focus. |

### 4.3.1 Total quality management

Total quality management (TQM) can be looked at as a combination of different concepts, which all contribute to a company-wide management of quality (Lau and Anderson 1998). It is up to the top management to apply these concepts according to the business conditions. Total commitment to quality, linking the business strategy to quality, continuous improvement and strong leadership in every level of the company are key elements in TQM (Table 3).

The implementation of TQM has been challenging due to its complex nature. Organization characteristics affecting the implementation of TQM were studied by Mann and Kehoe with the help of structured interviews (Mann and Kehoe 1995). They found that methods of manufacturing, skills of employees, shared values, management style, company's size and organizational structure affected the success of TQM. They emphasized that by identifying these factors implementation of TQM could be better tailored to the company's needs and a long term business success could be achieved.

Table 3. The concepts of total quality management (Lau and Anderson 1998).

| Total | Quality | Management |
|---|---|---|
| Employee participation and teamwork | Customer (internal and external) driven | Top management commitment |
| Everyone must develop a sense of quality ownership | Continuous improvement | Establish purposes and values for the company |
| Every level and function of the company is involved | Training for skills and knowledge | Leadership is critical |
| Apply systems thinking | Encourage innovations | Make appropriate change in organization culture |

Successful implementation of TQM, according to Taylor and Wright, was associated with the maturity of TQM, the understanding of the underlying purpose of TQM and its relations to other QMSs (2003). Benefits of TQM were significant when quality was part of the company`s strategic plan and strong employee involvement existed throughout the organization. The size of the company and the certification to ISO 9000 did not seem to have an effect.

### 4.3.2 Lean

Lean management is a Japanese concept created by Toyota. Its aim is to reduce waste and variability keeping customer needs in mind by continuous improvement (Andersson et al. 2006, Arnheiter and Maleyeff 2005). Just-in-time production methods and small batch sizes are typical for lean production. This results in higher flexibility while still productively producing quality products. Overall, lean management can result in both cost and time savings.

Elements, which are not adding value to the process or to customer, are eliminated. Outsourcing and subcontracting of activities is typical for lean management. Because of this, lean management is often linked with layoffs. This is a common misconception. Lean management concept is depended on multi-skilled workers who`s knowledge can be utilised and who are able to inspect their own work (Cusumano 1994).

### 4.3.3 Six Sigma

Six Sigma concept was developed in Japan for Motorola in the 1980s (Antony and Coronado 2002). It describes the capability of the process to produce products and implies that the defects occur at the rate of 3.4 defects per million opportunities. Six Sigma aims to eliminate defects by reducing variation and by investigating how these affect productivity and quality. This is done with the help of statistical and problem-solving tools, thus reducing quality costs (Antony 2004).

A survey to UK-based manufacturing and service organizations revealed the most important elements for the implementation of Six Sigma programs (Antony and Coronado 2002). Management involvement was found to be the most important aspect due to the nature of Six Sigma, which is a top to bottom business strategy. Understanding of the Six Sigma tools and techniques and linking Six Sigma to the business strategy and customers was also crucial to an effective implementation of the program.

Six Sigma can be seen as a methodology, which is part of TQM (Klefsjö et al. 2001). Six Sigma concentrates usually on fixing isolated processes and reduces its variation with regard to quality. Data gained from this method can deepen process understanding and thus supports other QMSs.

### 4.3.4 ISO

ISO (the International Organization for Standardization) standards are applied in different types of organizations regardless of the field of business (EN ISO 9000:2005). ISO standards can also be used together with other quality systems. Managing the quality system according to a certain standard can improve performance and address different needs of the organization and other interested parties e.g. authorities, user of the product and outsourced activities. There are separate requirements for QMSs (ISO 9000) and requirements for products (ISO 9001). The most suitable ISO standards utilized also in pharmaceutical industry include ISO 9000, ISO 9001, ISO 19011 and ISO 14000. From which ISO 9001 and ISO 14000 are the most registered system standards (ISO 2008). Own standards have been developed e.g. for food safety (ISO 22000), automotive industry (ISO 16949) and medical device sector (ISO 13485).

ISO has created an operations model for QMS (Figure 9) (EN ISO 9000:2005). Customers` and other interested parties` requirements and satisfaction are the foundation for this process-based approach. Inputs are transformed to outputs by utilising available resources provided by the management. To ensure the capability of the process and the quality of its products, the effectiveness and the efficiency of the process is measured and determined and continually improved so that customers' expectations are met.

The effects of having an ISO certified business have been shown in many studies. The results are both positive and negative. The benefits, which can be gained from ISO 9000 certification process, depend on the motivation and the quality culture of the company (Terziovski et al 2003). Customer focus and number of years being certified was found to be important factors affecting the quality culture and gaining benefits of ISO 9000.

Benefits to company's performance were less if external pressure was put on the company to implement ISO 9000 (Najmi and Kehoe 2000). Certification alone does not guarantee better business performance and improvements in performance can also be due to other factors involved (Singels et al 2001). Business performance has been studied with the help of performance indicators such as production process, company result, customer satisfaction, personnel motivation, and investment on means.

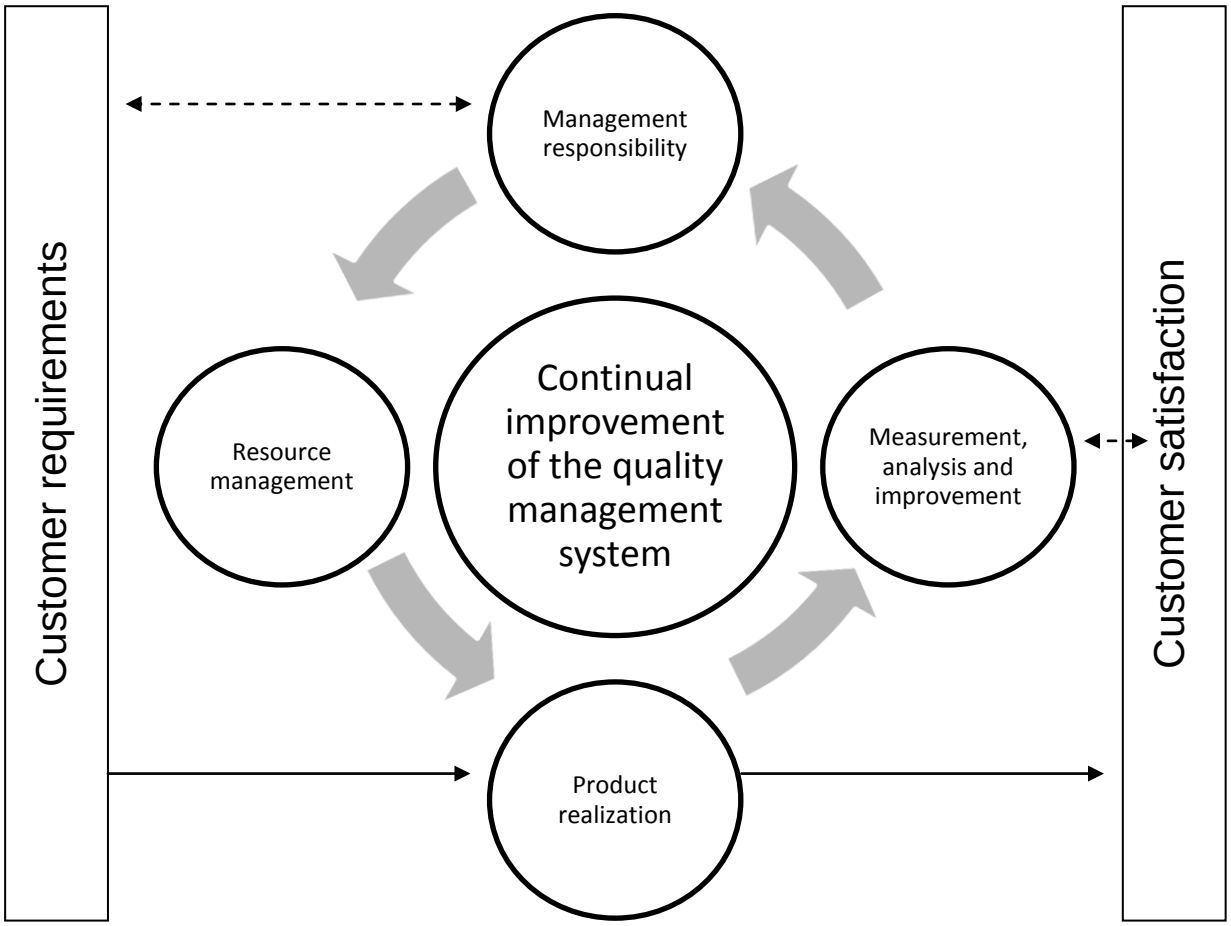


Figure 9. Process-based QMS (SFS-EN ISO 9000:2005).

### 4.3.5 European Foundation for Quality Management Excellence model

European foundation for quality management (EFQM) excellence model is the European Quality Award model for business excellence (EFQM 2010). It is a framework applied to manage quality with the help of self assessment. It consists of nine elements, which are divided into two sets of criteria, namely enablers and results (Figure 10). These criteria are linked together in the way that enablers drive results (Bou-Llusar et al. 2005). Cause and effect-relations between enablers and results must be established to gain the full benefit of this approach. As the results are measured, action needs to be taken to correct the right enablers in order to promote improvement. Leadership is said to be the main driving force behind quality award models (Wilson and Collier 2000).

With this quality management model current status of activities and results are compared with the EFQM framework and areas for improvement are recognised (Kaye and Anderson 1999). There exists multiple ways to execute self assessment and it is up to the company to realize it. Self assessment often includes measurement of activities and results and improving systems based on these measurements. This will ultimately drive the business towards excellence.

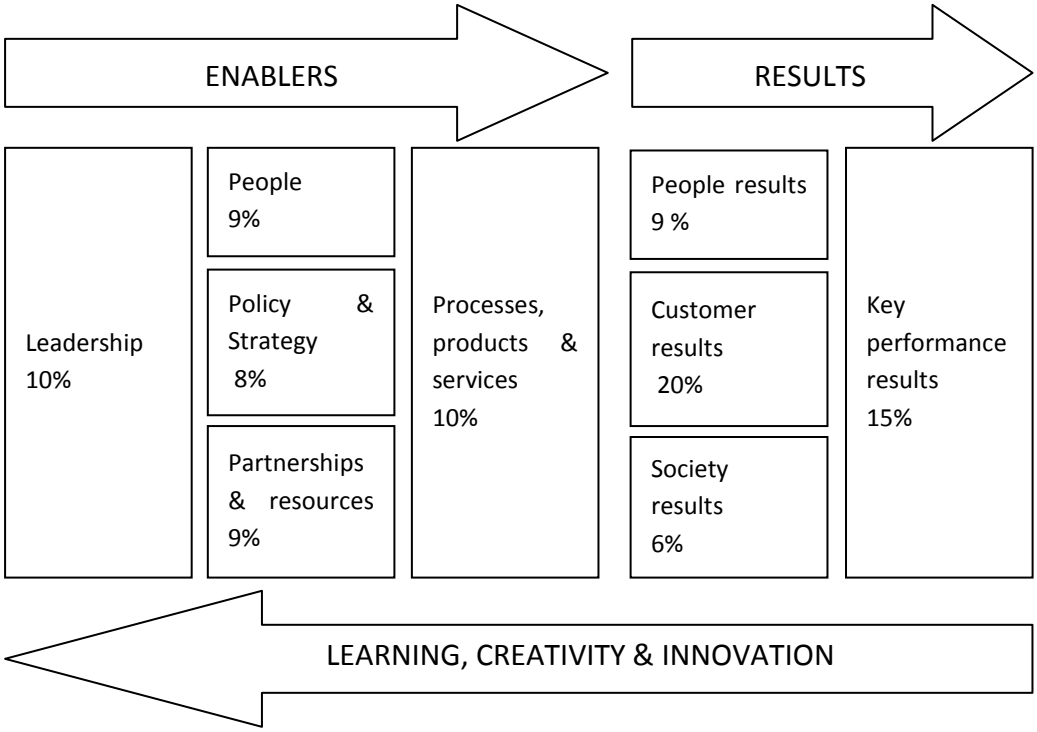


Figure 10. EFQM Excellence model (EFQM 2010).

## 4.4 Pharmaceutical quality management systems

QMS in pharmaceutical field differs from the other QMSs by being safety-oriented whilst the other QMS are more customer-oriented. Quality system is mainly needed for three reasons: in order to manage quality, to ensure compliance and for improving consistency throughout the organization (Ricci and Fraser 2006).

Good Manufacturing Practice (GMP) gives guidance and lays the foundation for the quality systems in pharmaceutical manufacturing industry (GMP Chapter 1, Markovitz 2010). GMP guidance is applied by pharmaceutical industry to achieve quality goals and to maintain QMS. Also the quality systems mentioned previously are used in the pharmaceutical field.

### 4.4.1 Laws and regulations

Pharmaceuticals are one of the most regulated products in the world (Vogel 1998). Nearly all aspects of pharmaceutical products are monitored by the regulatory authorities from the development and manufacturing stage all the way to the pricing and distribution of the product. The need to regulate this field rises from the concern of the safety of the product and the central role these products have on people's health. Due to the nature of pharmaceutical industry, regulations tend to be very strict. The regulatory authorities have the consumers' best interest in mind, as the consumer cannot evaluate the quality of the product. Breaches of any regulation can lead to public mistrust and penalties from regulatory authorities. Regulations should always be of more of advantage than an economical burden (Deming 1982).

Pharmaceuticals are manufactured and marketed globally (Vogel 1998). This adds the amount of regulation. Some of the major authorities, which companies co-operate with, are the Food and Drug Administration (FDA) in the USA and European Medicines Agency (EMA) in the EU area. In addition to this, harmonised guidelines (ICH) and local authorities and laws (e.g. FIMEA) have to be considered.

Legislations and guidelines for pharmaceutical industry have been formed over the years and were influenced by incidents in the field of chemistry, pharmacy and food supplies (Arayne et al. 2008). Official standards for the strength, quality and purity of drugs and the labelling of the products were demanded in the beginning of the 20$^{th}$ century. This was due to incidents concerning contaminated biological products and food. Legislation was also formed to ensure that products had to be proven safe before marketing them. The authorities (FDA) started to demand quality control for drug products and this led later to the formation of GMP-guidelines.

Nowadays, regulatory authorities try to direct their actions to prevent incidents from occurring rather than responding to incidents. Increased attention is given to quality and risk management systems as this increases the company's own knowledge about their processes and helps them to keep these processes under control (Poska 2010).

Legislation, guidelines and inspections have been an important part of regulating and investigating the manufacturers of medicinal products (Arayne et al. 2008, GMP Chapter 1). It is the holder of the marketing and manufacturing authorisation, which is responsible to ensure the quality and safety of their product, not the regulatory authorities.

### 4.4.2 Good Manufacturing Practice

GMP is an international set of regulations and is part of quality assurance, which sets requirements for quality systems and minimum level of quality management within pharmaceutical industry (Arayne et al. 2008, GMP chapter 1). Other quality systems can also be utilised in the pharmaceutical industry to get an effective QMS but these are not required by the regulatory authorities (ICH Q10). It relies on certain requirements which have to be fulfilled in order to ensure that the product matches the specifications and the marketing authorisation set for the product (Table 4). GMP assures the quality, safety and effectiveness of the product by ensuring consistent production and control of the products (GMP Ch 1).

Table 4. GMP requirements (GMP Ch 1).

| **Requirements for GMP** | |
|---|---|
| • clearly defined manufacturing processes | • **having an efficient recall system** |
| • validation of critical process steps | • **dealing with complaints** |
| • providence of appropriate facilities | • **training of the operators** |
| • written instructions and procedures | • **making of the records** |

### 4.4.3 International Conference on Harmonisation

The International Conference on Harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) standardises and rationalises the requirements of the regulatory authorities from Japan, US and Europe (ICH 2010).

Regulatory authorities and industry have decided to work together towards gaining a harmonised and improved process for developing and registering medicinal products with harmonised ICH guidelines, which include quality, safety, efficacy and multidisciplinary guidelines. ICH guidelines are not regulatory requirements in themselves, but are meant to complement regional GMP (Drakulich 2008). ICH Q10 guideline shows a framework for a model for pharmaceutical quality system (Figure 11).

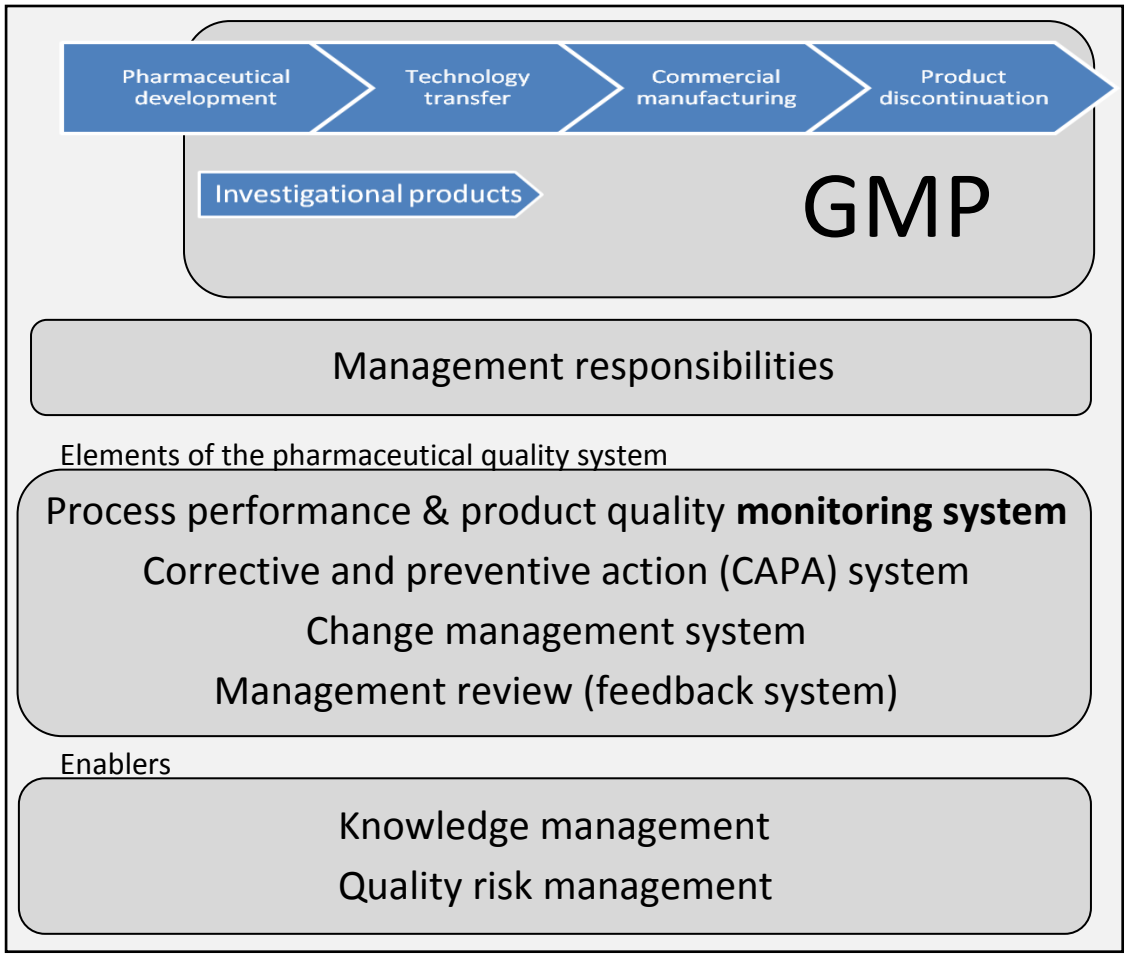


Figure 11. Principles of ICH Q10`s Pharmaceutical Quality System model (ICH Q10).

This QMS emphasises the responsibility of the management and the need for continual improvement of the quality system (Van Arnum 2007). The elements of quality system can be used in different stages of product lifecycle and this strengthens the link between

development and manufacturing activities. GMP is mostly limited to manufacturing environment, but QMS is company-wide. Established knowledge and quality risk management enable full use of the quality system.

The objectives of ICH Q10 are to establish a state of control, help achieve product realisation and to facilitate continual improvement (Van Arnum 2007). Continuous improvement can consist of eliminating waste, saving costs and streamlining systems. Quality risk management from ICH Q9 can be utilised at different stages in QMS. It can help determine which actions to monitor and which improvements to make.

# 5 ELEMENTS OF THE QUALITY MANAGEMENT SYSTEM

As stated in the previous chapter, QMS consists of interrelated elements which are described in this chapter in more detail. These elements are needed to establish maintain an effective QMS. The functionality of QMS can be measured, monitored and improved such as any other process or system. This ensures better control of quality and can improve performance and quality even further (Low and Omar 1997). Approaches used to monitor and manage QMS are shown in Figure 12. Some technical approaches include feedback systems, internal quality audit, training, control of documents and quality records and management review. Giving that there is availability of information, support and resources also non-technical approaches can be taken. These consist of communication across different levels in the organisation, utilisation of teamwork when it comes to problem solving and quality improvements, to motivate employees and to get them to participate on quality related matters, emphasis on training and feedback.

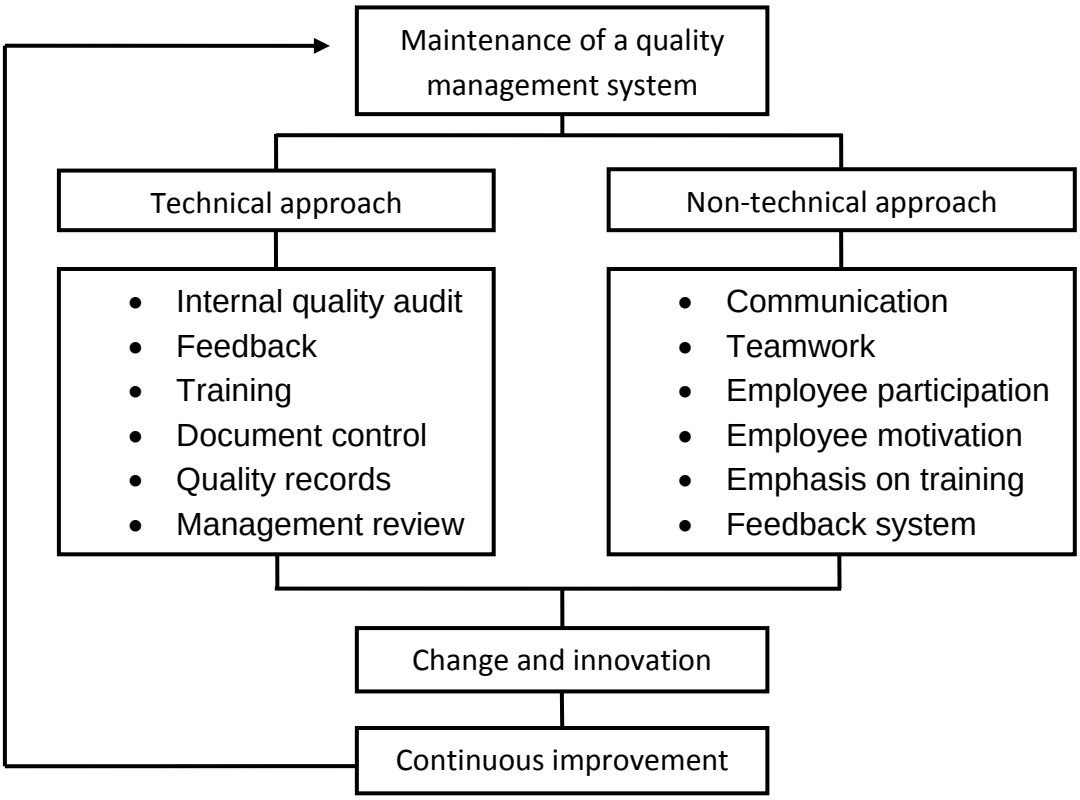


Figure 12. Approaches for QMS maintenance (Low and Omar 1997).

To begin with, all quality related activities have to be defined and documented to be able to manage them (ICH Q10). Also the infrastructure of the company needs to be clear and the responsibility to monitor and maintain these different elements of QMS need to be comprehensible. Any management system, which needs to consider safety, can be further strengthened by risks assessment (Adis 2008). Internal audit is an important part of the QMS (Probitts 2000). Audits will be discussed in more detail in the next chapter. In Figure 13, it is displayed how internal audit itself is part of QMS. It also illustrates how audit is commensurate with other elements of QMS, which are further discussed in this chapter.

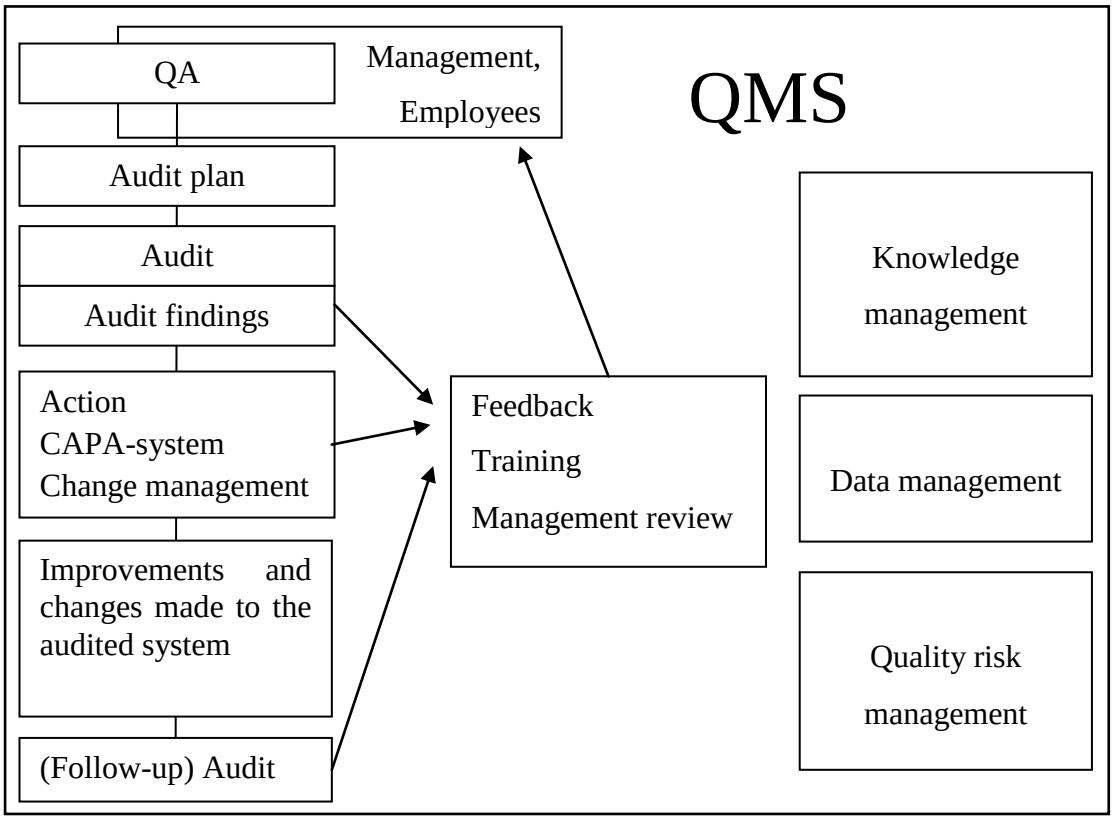


Figure 13. Audit and other elements of quality management system.

Audits should be well planned and executed to reveal issues for improvement and correction. This is done by people committed to quality-related issues (QA). Further action is taken to realize improvements in the form of corrective and preventive actions and change management. A feedback system helps the organisation to learn from data and information gathered by audits and actions to audit findings. This feedback of

information can also reach management attention to direct more resources to detected problem areas. Follow-up audit can be done to ensure that implemented improvements have been successful.

## 5.1 Quality units

Quality units in pharmaceutical industry consist of people or departments fulfilling the duties concerning quality-related matters in accordance to GMP guidance. Quality assurance (QA) and quality control (QC) are such units as they ensure that systems are planned, approved, conducted and monitored appropriately (FDA, Edwards 2008). QC detects and controls faults by making tests and QA prevents deviations by investigating, and resolving problems related to the quality system (Schindel-Bidinelli 1996). In pharmaceutical industry companies have set internal standards and limits to control their processes and these are managed by the quality units with quality assurance techniques (Adis 2008).

### 5.1.1 Quality assurance

Quality assurance (QA) activities in a company are important when it comes to ensuring compliance with quality systems and regulations (Hettemer-Apostel 2007). The goal of QA is to develop quality and compliance standards and to design a quality system (Skubch and Zimmer 2009). As can be seen from Table 5, the more traditional parts of QA`s duties are obligatory in nature, such as monitoring and reporting. Optional tasks include a different outlook on quality related issues in the form of providing tools to assure quality and having more of a consulting role. QA conducts audits and reports the relevant findings to senior management. QA also has a supporting function as it has a key role in sharing information, suggesting improvements, and giving its input on quality related issues.

QA activities include auditing, inspections of the facilities, training staff and managing standard operating procedures (SOPs) (GMP Ch 1). QA relies on principles and policies set by the company management and QA makes decisions based on data from different

departments, SOP, protocols, guidelines and regulations (Jones 2002). QA`s limited resources should be focused on the most critical areas in a process or field of business.

Table 5. Tasks of QA (Skubch and Zimmer 2009)

| Tasks | In detail | Obligation |
|---|---|---|
| Define | Develop strategy, policy and standards and specified instructions on operational level | Mandatory |
| | Specify tools, systems and underlying architecture | Optional |
| Control | Monitor (audit) implementation progress and proper application in the daily business | Mandatory |
| | Report performance level and major deviations to the Executive Board | Mandatory |
| Support | Provide communication platform to enable know-how exchange and continuous improvement | Optional |
| | Facilitate correct use via consulting, counselling or training affected staff | Optional |

QA functions as an independent group within the organization (Feldman 2005). Development, manufacturing and quality units have to cooperate but their functions have to be independent from one another. This is necessary to achieve a good and thorough analysis of the developed systems and manufacturing processes. Keeping these functions separated enables a neutral analysis and removes bias. There are also problems due to this separation of the important functions. People working in QA have to have expert knowledge and a deep understanding of the process they are inspecting. Otherwise, it might lead to friction between the departments, if a mutual understanding is not reached.

### 5.1.2 Quality control

Quality Control (QC) is involved in detecting and controlling of faults within GMP-environment (GMP Ch 1). This includes sampling, inspecting and testing of materials, and dealing with specifications and procedures to ensure that all required tests are done (and Ch 6). QC is also involved in ensuring the quality of the materials and products

before they can be released and checking the composition and purity of the drug product and ensuring appropriate package material and labelling.

### 5.1.3 Qualified person

Qualified person (QP) is recognised only in Europe and according to European GMP it is a requirement to have a QP at a pharmaceutical manufacturing site (GMP Ch1). QP is in charge of quality-related decisions regarding the certification and releasing of the batches for sale. QP is also responsible for pharmacovigilance (Talbot and Nilsson 1998) and the review of quality related complaints and a possible recalls of deficient products from the market (GMP Ch 8). QPs can also participate in internal audits and take audit findings into consideration when assessing the quality of products and systems.

## 5.2 Data management

“Loss of quality in data can lead directly to a loss of quality in products” (Fowler 1995). The role of data management is important in manufacturing environment especially because of its link to quality aspects. Data is gathered about products, processes and other functions at different stages of product`s life cycle and this data needs to be easily accessible and shared through the entire organisation to support effective decision making. It is important that imprecise data is not used for decision making as this may lead to unnecessary or poor changes, which may affect the cost and quality of the product. Information technology (IT) supports the collection and management of data and information securely (Nollau 2010). Uniform IT-systems aid in data transfers within the organization. Collaboration between IT and quality units is essential for a successful business.

The ideal goal of product data management can be seen as a system “which ensures that the right information in the right form is available to the right person at the right time” (Liu and Xu 2001). Data management systems can be created to gain this goal. Product data management system can lead to easier access to information, reduced cycle times,

increased collaboration between departments through sharing of information and faster problem identification. The downside with product data management system is its inability to react rapidly to changes and its complex nature, which often makes it so time-consuming to learn to use.

The main reasons for documentation in pharmaceutical manufacturing environment are due to the safety issues concerning the use of medicines (Sharp 2000). Documentation is done firstly to ensure and to confirm that procedures and processes are carried in accordance to plans and set quality standards repeatedly. Secondly, if complaints are received, defects occur or deviations are observed, it is important to be able to trace back (with the help or documentation) what has been done and find the cause these incidents. This way corrective and preventive action can be taken.

Documentation plays an important role in internal quality audits and regulatory audits (more about these in the next chapter) as these both often use documentation as a starting point and as evidence when looking at how things have been done and comparing it to how it should be done or how it is practically done. Documentation makes the actions of the company visible and there is a saying that “if it is not in writing, it has not been done”.

### 5.2.1 Role of documentation which guides the operations

Documentation is important part of QMS and GMP, since written documents and procedures guide operations, record what has been done, and help to give feedback. It is important that documentation is in-line with regulations and quality standards, because measurement (e.g. audit) of the functionality of QMS or a process is often done against these documents. Also it is presupposed that the whole QMS itself is well documented. This documentation is shown in Figure 14 and it exists in three levels. Quality manual is a document, which describes the entire QMS (Biazzo and Bernardi 2003, SFS-EN ISO 9000:2005). It includes information on how QMS is planned (quality plans) and what are the requirements for quality (specifications). It should also take into consideration any regulative guidelines. Quality manual often refers to quality procedures and

standard operating procedures (SOP) concerning vital processes of the company. These procedures describe how to carry out these processes in detail. SOP should always reflect how things are actually done. Not just what should be done. Records are being made as operations are on-going. These records include e.g. analysis results and data about the performance of the process.

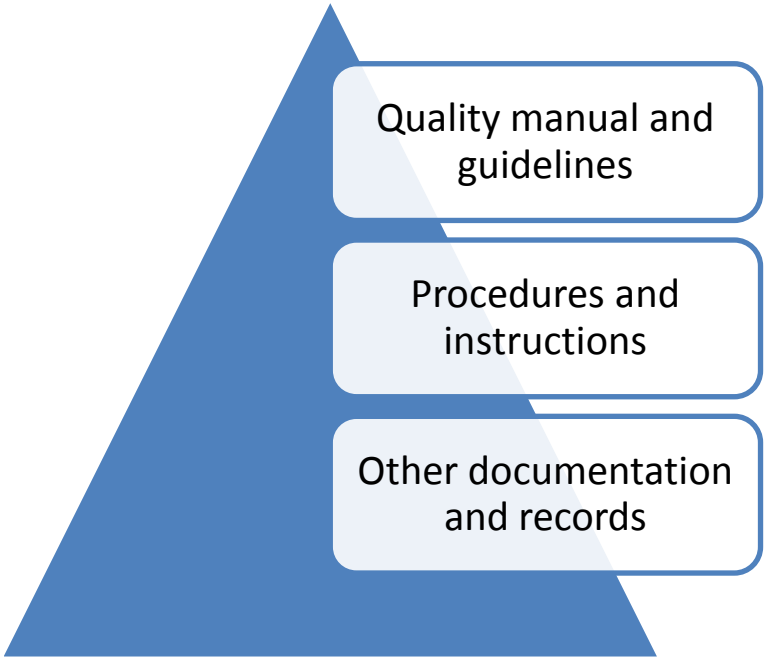


Figure 14. Documentation of quality-related activities (Adapted from ISO 9000:2005, ISO 9001:2008)

### 5.2.2 Product quality review

Product quality reviews should be conducted annually (GMP Chapter 1). This document considers the medicinal product`s quality and the consistency of the production process and review all the quality-related documents over a set period of time. Change and CAPA activities are analysed in the review. Product returns, complaints and recalls related to quality are also considered. Product quality review can indicate trends and needed improvements (GMP Ch 1). CAPA activities can be suggested based on product

quality review and the implementation of these can be investigated with the help of internal audits (self-inspections).

### 5.2.3 Management review

Management review is done to ensure continuing suitability of process performance, product quality, and quality system (ICH Q10). Management review includes the results of inspection and audit findings, complaints and recalls related to product quality, effect of process and product changes and conclusions regarding the monitoring of process performance and product quality. Improvements to quality system and processes can be suggested based on this review. Senior management can base its decisions on management review and implement necessary changes.

## 5.3 Knowledge management

Knowledge is an important resource and part of company`s "strategic capital" (Berawi 2004, Deming 1982). If it is utilised and managed well, it can even improve quality management. Knowledge should be shared through open communication to integrate best practices throughout the whole company (Lubit 2001). Knowledge should be securely and effectively stored and transferred inside the company. Strategic decision making, finding the root cause for a problem, and understanding of common goals can be gained with a knowledge management system.

Knowledge management can be defined as "a managerial activity which develops, transfers, transmits, stores and applies knowledge, as well as provides the members of the organization with real information to react and make the right decisions, in order to attain the organization's goals" (Hung et al. 2005). Knowledge management systems can be formed to effectively manage knowledge. Other ways to manage knowledge, such as measuring or audit, are difficult to execute. This is why a proactive approach is important when it comes to knowledge management. Employee participation and management involvement are key factors in implementing a successful knowledge

management system and the most important enabler is the use of information technology (Wong 2005).

## 5.4 Quality risk management

Risk is defined as a potential harm, which has certain probability of occurrence and a level of severity (ICH Q9). Risk management should be used as a tool to identify, control and reduce risks (GMP Chapter 1, Adis 2008). The principles concerning risk management are used in many areas of business. The quality risk management and assessment should be utilised more widely in pharmaceutical field because of strong focus on safety. It should be used as a systematic process to review the risks of the product, process and the quality system. Managing risks should be based on scientific knowledge so that it can guide effective decision making. Risk management can be both formal and informal and it can be applied proactively and retrospectively.

Both industry and regulators apply risk management principles and tools to direct actions towards the important and complex aspects of their business more effectively (Edwards 2008, ICH Q9). Quality risk management can be part of the QMS and help determine contents of SOPs, required amount of training to personnel, to detect quality defects, define frequency and scope of audits and to manage change and drive improvement. Many aspects of product`s lifecycle should be based on risk assessment and management. Risk management is also acknowledged by the regulatory authorities and is mentioned in the current GMP (GMP Ch 1, Adis 2008). Regulatory authorities use quality risk management to determine inspection activities.

The design of a risk management system should consist of risk assessment, control and review and it should also include risk communication (Figure 15) (GMP Ch 1, ICH Q9). The system should take all the important elements of the analysed area in to account and this should happen at a level of detail, which is commensurate with the level of risks involved. There are many tools for pharmaceutical quality risk management, which can be used in combinations with one another. As a result of the risk assessment, a quantitative estimate of risks, a qualitative description of risks or an overall estimate of

relative risks is achieved. Detected risks can be reduced or accepted. The importance is that their impact is taken into account.

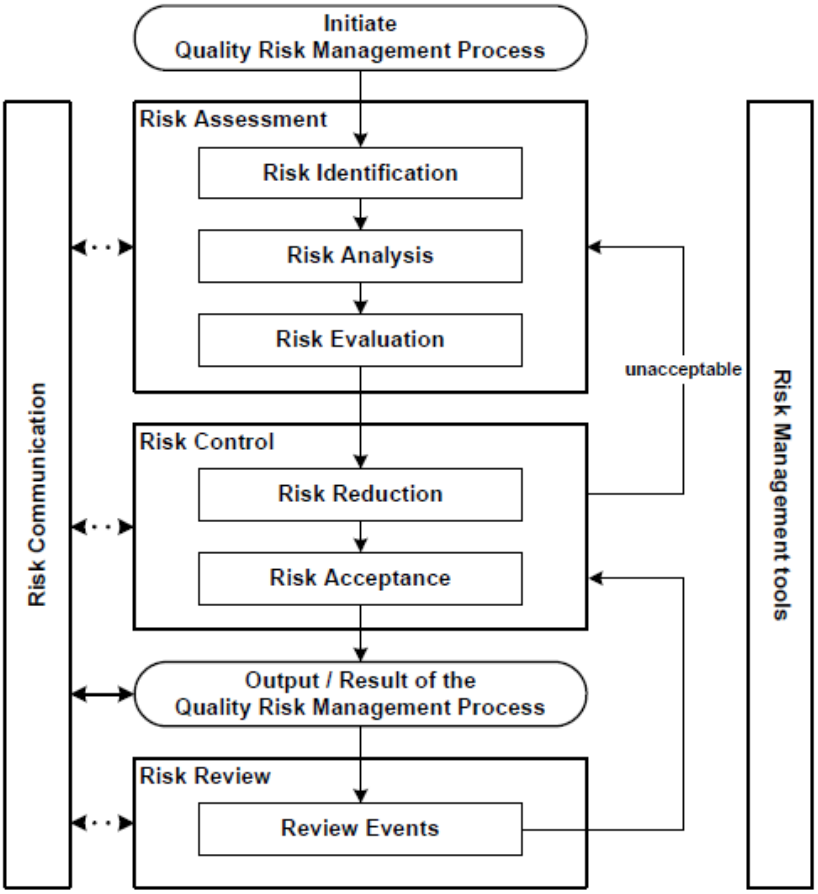


Figure 15. Quality risk management (ICH Q9)

### 5.4.1 Risk management tools and techniques

Risk management tools and techniques can be utilised throughout the risk management process. Failure Mode Effects Analysis (FMEA) and Hazard Analysis and Critical Control Points (HACCP) are the most utilised risk management tools in pharmaceutical field and these are used to identify potential failures, which can affect the performance of the process or the quality of the product (ICH Q9, Onodera 1997, Skubch and Zimmer 2009).

Product and process understanding is crucial when conducting FMEA. It can be applied through the whole life cycle of the product and it can be particularly useful in prioritising risks. Failure Mode, Effects and Criticality Analysis (FMECA) is a modified version of FMEA and takes the risks more in to account by dealing with the severity, occurrence and detectability of occurred failures. FMECA can give a relative risk score for failures and raise focus on where preventive actions should be taken. HACCP is widely used for product safety assurance and it was originally developed to ensure microbiological, chemical and physical safety of food (WHO, ICH Q9). HACCP is a systematic management tool aimed to identify and prevent hazards and to manage risks. This is done by conducting a hazard analysis and determining critical control points of the process. Critical control points are monitored so that preventive action can be taken when the set critical limits are not met.

Other commonly used risk analysis tools in manufacturing industry include Hazard Operability Analysis (HAZOP), Preliminary Hazard Analysis (PHA) and fault tree analysis (FTA). HAZOP is a review of deviations in a system (ICH Q9). It is a qualitative risk assessment tool, which uses a brainstorming technique to identify hazards. It can be used to evaluate process safety hazards and to list critical points in operation. PHA tries to identify and predict hazards. Prior knowledge is used to discover and estimate future hazards and to prioritise them. FTA is a tool to evaluate failure paths and identify root causes as it combines causes of failure in a visual diagram. FTA relies on process understanding to establish these causal chains and this makes it possible to analyse complex systems and identify relationships between contributory factors in the system.

Statistical tools and brainstorming can support risk management. Statistical tools can consist of different types of control charts, which visualise and show the data in a more clarifying way (ICH Q9). Design of experiments and process capability analysis are also helpful statistical tools. Brainstorming can be a great tool in problem solving and finding causes for risks from different perspectives. These methods can help with the assessment of data and ease decision making.

## 5.5 Implementation of improvements and corrections

It is important to have the means to monitor own systems and to take time and find the root cause for the problem, rather than finding a quick solution. It is also crucial to have an effective system to implement these corrections and changes. This is done with the help of Corrective and preventive action (CAPA) system and change management.

### 5.5.1 Corrective action and preventive action system

CAPA system can implement the wanted changes (ICH Q10). The suggestions for these changes can come from audit findings. Corrective actions in CAPA mean concentrating on solving the actual problems (Markovitz 2010). Preventive actions consider dissolving the arisen problems. Many companies use time and resources to identify problems, and to find quick solutions to fix these problems. More time should be used to actually resolve the problem by finding the root cause. Optimising the system to prevent future failures and deviations gives long term benefits of the CAPA system. The corrective actions are often a weak area in QMS and by improving them, the whole QMS could become more effective (Gupta 2006).

### 5.5.2 Change management

Common sense should never be the reason for taking action and changing a system (Deming 1994). Making hasty decisions about improvements may lead to serious consequences. Changes have to be managed because they can critically affect the process and the product quality (Buecker and Tuttle 2002). Change management is a formal documented process where the change is justified, approved and implemented. Innovations, continual improvements, CAPA and audit findings drive change management and promote continuous improvement (Figure 16, Drakulich 2008). The aim of change management in the pharmaceutical field is to safely improve systems and processes, rather than to control change. Risks involved with the change have to be assessed and the change has to be thoroughly evaluated and communicated before its

implementation (ICH Q10). If a design space is established, changes to a process can be done more flexibly, but they still need to be managed.

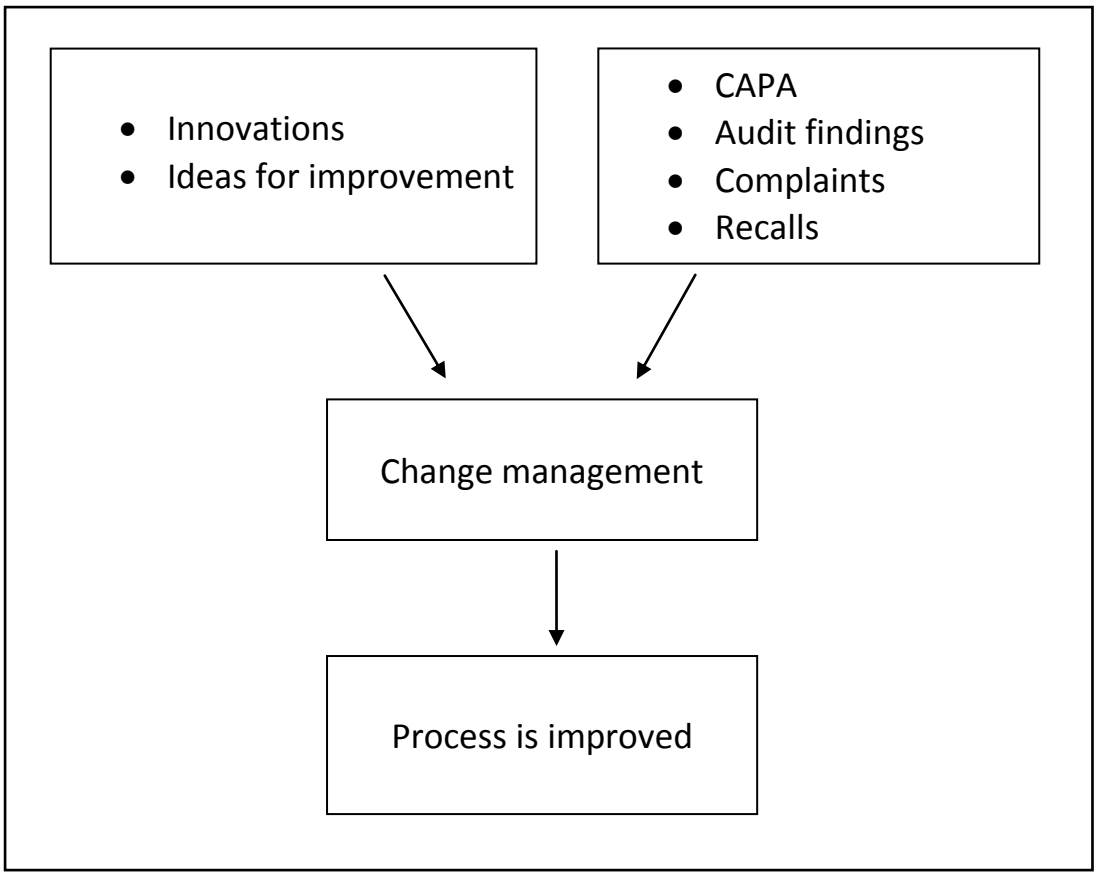


Figure 16. The inputs and outputs of change management

# 6 INTERNAL AUDITS

Besides the elements mentioned in the previous chapter, internal audit is a pivotal part of QMS. Operational systems, management and all the supporting elements have to be in place in order to manage quality systems effectively (Gupta 2000). In this chapter a definition is given to internal audit and its role with regard to QMS and operational systems is determined. Different types of internal audits and other types of audits are briefly presented and compared with internal audits. Internal audit procedure and techniques utilised by internal auditors are explained and the possibilities to utilise internal audits are discussed.

## 6.1 Definition of internal audit

Audit is an important tool for monitoring and managing quality, performance and business systems (Karapetrovic and Willborn 2000, Skubch and Zimmer 2009). Internal audit according to ISO 9000 is a "systematic, independent and documented process for obtaining audit evidence" for internal purpose (SFS-EN ISO 9000:2005). It also includes an objective assessment of gathered audit evidence against audit criteria. The Institute of Internal Auditing has pushed the definition of internal audit even further when they claim that, in addition to the previous definition, internal audit should be an "objective assurance and consulting activity designed to add value and improve organization`s operations" (Nagy and Cencer 2002). This is an aim towards continual improvement and demands a more active role from the auditor side to use internal audits as a tool to develop processes. Just by looking at the diverse definitions of internal audits, it can be stated that internal audits can be tailored to meet company`s needs. Internal audit can also be adapted according to changing demands and can offer a more comprehensive approach compared to the traditional method of inspecting.

## 6.2 History of auditing

Auditing has its origins in examining accounts and records in the form of a financial audit (Arter 2003). Due to technology improvements; the military, automobile industry

and nuclear plants started to apply audit to their own functions and subcontractors. Later the governments started auditing regulated and complex businesses, and to audit their own systems. In addition to the financial audit function, audit was also used as a tool to manage risks, and control manufacturing processes. As business became more global, quality auditing and common standards were established. Audit was widely adopted in many fields of business to ensure compliance to management systems.

## 6.3 Role of internal auditing today

The traditional form of auditing has been associated in a negative way as an inspection, which is considered a requirement and where deviations and faults are dig up as work is badly disrupted (Morris 2008). Today audits consider the positive sides and strengths of the organisation alongside with nonconformities and auditing has become an important source of information in complex business fields where adaptation to changing environment and requirements is crucial to be able to cope with the competition (Karapetrovic and Willborn 2000, Percy 2010, Taormina 1999). Internal auditing ensures compliance, suitability and effectiveness of QMS and it aims towards continual improvement. Internal audits can observe that processes are operating according to documented procedures, implying that relevant procedures exist and they are followed.

In the innovative and complex environment of pharmaceutical industry, internal audits can be looked at as a learning experience, as these deepen knowledge about own systems and processes (WHO Annex 4). It is stated in the GMP that internal audits should monitor the implementation of and the compliance with GMP and also generate suggestions for corrective actions (GMP Ch 9). This indicates that internal audit is more than just an inspection, it can be considered as an improvement tool. When it comes to the pharmaceutical field, internal audits are considered as GMP-requirement to objectively evaluate company's own functions. This emphasizes the importance of such audits in ensuring quality of pharmaceutical products.

### 6.3.1 Internal auditing from the management point of view

Management can use internal audits as a tool to monitor, evaluate and improve complex systems which they are responsible for (ICH Q10, EN ISO 19011:2002, Sawyer et al. 2003). Audits should be planned according to management objectives and organizational strategies and it should be looked at as an investment, which has the potential to improve business (Kausek 2008). Internal audits can also proactively identify and minimize risks (Fadzil et al. 2005). Internal audit reports help the management to make decisions based on information gathered by internal auditors. Strong links of communication and co-operation should be established between auditors and managers of the audited field to support the overall audit process (Beckmerhagen et al. 2003).

If an audit is ineffective, it is often due to poor management of the quality system (Gupta 2000). Audit does not fix all the problems, it only points them out. Management needs to have an active role in directing focus and taking action to audit results. Otherwise, full benefit from audits cannot be reached. There has to be an effective CAPA system present to improve the audited system. In this manner audits can help prevent mistakes and improve systems.

### 6.3.2 Value of auditing

The new definition for internal audits stated that internal audits should add value (Nagy and Cencer 2002). Internal audit has not always been perceived as adding value, though it has been considered necessary (Elliot et al. 2007). Value of internal auditing process to business performance has been considered to result from improving processes and thus adding value for the company by saving money and resources (Fadzil et al. 2005).

In a survey study directed to the management, auditors and auditees of ISO standardised company, positive and negative effects of internal audits were studied (Alic and Rusjan 2010). Internal audits had positive effect on the work with customers (better communication, meeting regulatory requirements, and better quality of goods),

implementation of processes (organization of work and increased productivity), learning (better skills and sharing of good practices) and the financial performance (decreased damage, savings due to improvements). Among the negative effects was the cost of conducting an internal audit. Internal audits were sometimes seen as obstacles to work-process and they also had negative effect on the relationship between auditors and the audited. In its entirety internal audits were found to have more positive than negative effects on the business performance.

## 6.4 Different types of audits

Audits can be classified into internal and external audits. External audits are usually conducted by regulatory authorities or by business partners and internal audits are carried out within the company (Probitts 2000). Audits can be further categorized based on what is being audited and what is the goal of the audit. Compliance audit is the traditional way to conduct audit and with it conformance to set requirements is ensured (Ramly et al. 2008). Management audits can be used to systematically evaluate any management system (Askey and Dale 1994). It also can take into account the efficiency and effectiveness of the audited process and possible areas for improvement. Such audits are for example, audits of own operational processes and products, and QMS audits (Figure 17). Also the environmental, safety, financial and ethical aspects of business can be audited (Vinten 1998).

Besides the type of audit, there are two main approaches in conducting audits: vertical and horizontal approach (Jeronic 2010). The approach is chosen based on the purpose and scope of the audit. A vertical approach allows deeper inspection of one particular area, product or part of a process. A horizontal approach can follow the whole process from start to end and it also takes into consideration different interdependencies in this process. Quality system audits and process audits are usually horizontal in nature. The horizontal approach is usually done to get “an overall indicator of the performance and gaps in the organisation” (Kausek 2008). The vertical approach is used more frequently to gain detailed knowledge of the performance and the reasons behind possible gaps. Also a combination of vertical and horizontal approach can be done e.g. by conducting

an audit with the same topic to all the sites and/or departments. This is vertical in nature as it is one specific audit in a department, but also has some horizontal aspects as it sweeps through the whole organisation. Routine audits are done according to an audit plan. Special audits and follow-up audits are conducted when certain problems or faults occur with the quality or the efficacy of the system or the product, or the efficacy of corrective action needs to be confirmed (Taormina 1999). Audits can be formal or informal.

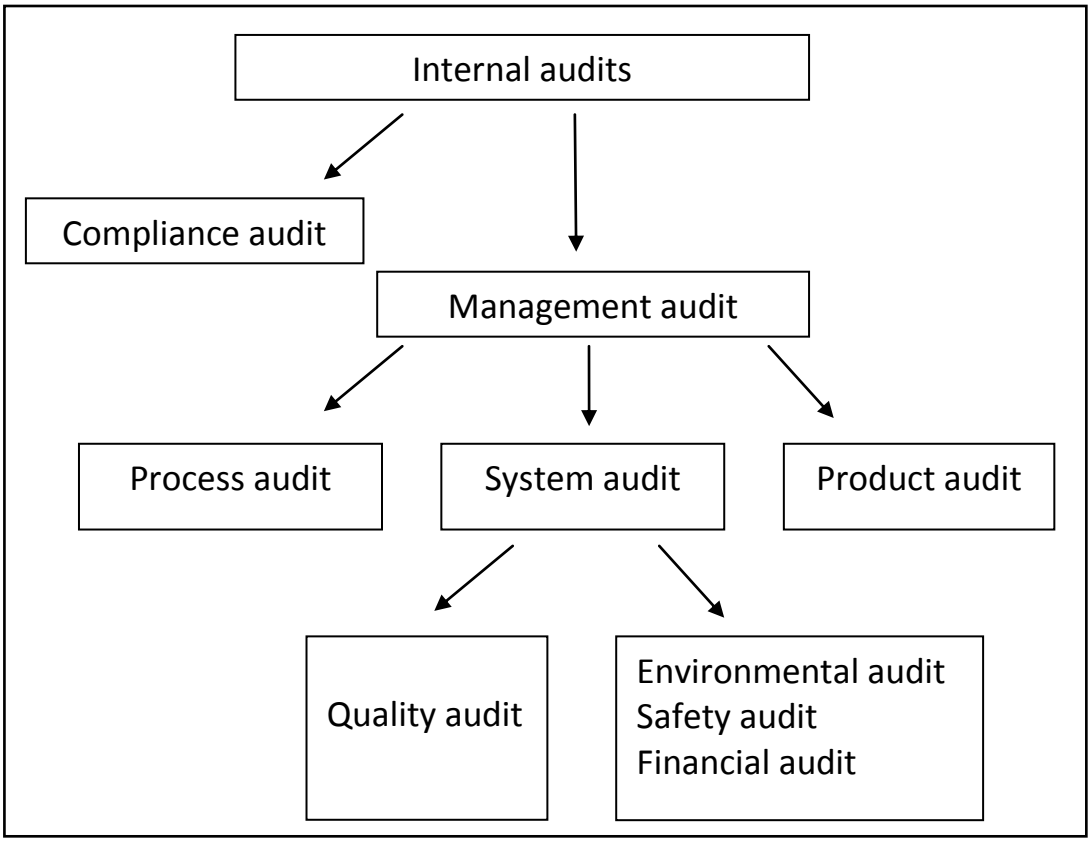


Figure 17. Different types of internal audits (adapted from Karapetrovic and Willborne 2001, Ramly et al. 2008)

### 6.4.1 Internal process, product and quality audits

Process audit covers all the important aspects of a process and follows the process from beginning to end (Sawyer et al. 2003). The efficiency of the process and cooperation with departments can be evaluated. Any differences and misconceptions between

different departments can be identified and common goals can be achieved as a result from the functional process audit. Audit of a product is more of a tollgate inspection, which can lead to product repairs (Gupta 2000). Audit of the manufacturing process can lead to correction and improvement of the whole process and this way ensures the manufacture of a quality product.

Internal audit programmes can reveal the condition of the QMS (Jeronic 2010). The traditional way to conduct the quality audit would be to ensure compliance with the implemented QMS and ensure conformity with quality standards. In a mature quality culture with established QMS, internal quality audits can also contribute to business performance by improving the achievement of business goals and efficacy (Alic and Rusjan 2010).

A company can have separate audit systems for different parts of their operations and management systems or they can have a single audit system, which is integrated and covers all that is to be audited within one field (Bernardo et al 2010). Internal audits can also be integrated to audit the entire management system, not only QMS, but also the financial, safety and environmental systems (Karapetrovic and Willborne 2000). The level of integration varies with the integrated components of the audit; objectives, resources and processes. This means that there can be a common audit plan, which is realised by a single audit team using predetermined methods resulting in a systemic audit report.

### 6.4.2 Self-audit and self-assessment

An example of an informal audit is the self-audit (Karapetrovic and Willborn 2002). Auditees or departments perform the audit themselves and evaluate their own work. This kind of audit is based on the idea that the auditee has the expert knowledge of the system and takes own initiative to improve it. This does not give as objective audit as an internal audit, but this method can reduce the amount of formal internal auditing in a company. Self-audits can also help to improve the process by evaluating it against set standards. The downside of this type of audit is that auditees don’t have as good

knowledge about the audit criteria compared to internal auditor and they may not have as good overall view about the company's objectives as auditors. Self-audit is similar with self-assessment, which is utilised in the EFQM Excellence Model. The main difference between internal audit and self-assessment is that audits are more concerned with the current compliance to standards and self-assessment is more future-oriented as it identifies strengths and weaknesses to find opportunities for improvement (Karapetrovic and Willborn 2001).

### 6.4.3 Regulatory inspections

Regulatory authorities (e.g. FDA, EMA or FIMEA) conduct inspections of pharmaceutical manufacturing sites. They focus on GMP-compliance inspections and marketing authorisation or pre-approval inspections. Before regulatory authorities conduct inspections on-site, they review the manufacturer's site master file to prepare for the audit (PIC/S 2010). Site master file has all the information about the pharmaceutical operations carried out on the manufacturing site, including quality assurance and the production.

FDA`s inspection is based on a system-based model and quality system has a fundamental role in it (Figure 18, FDA guidance 2006). It also takes in to account the relationship between different areas of the manufacturing system. Variability should be reduced through process understanding in these different areas. If one of the six systems is found to be out of control, the whole manufacturing site can be considered to be out of control because these systems are overlapping (Edwards 2008). Audit findings are presented as FDA 483 observations or as a warning letter (DeVito et al. 2006).

### 6.4.4 Audit of clients

Pharmaceutical companies have to do a lot of collaboration with other companies such as suppliers and contractors. Raw materials are often manufactured or supplied by others and development, manufacturing and laboratory analysis can be outsourced to save costs (Carter-Hamm and Vinson 2002). Quality and compliance audits to

outsourced companies e.g. contract laboratories, contract manufacturers and suppliers are done to ensure the safety of the raw materials used in production, safety of the product and accuracy of analysing methods, which the company is responsible for (WHO Annex 4). A pharmaceutical company, depending on its activities, may be the one performing the audit and ensuring the quality of outsourced work or be the target of an audit done by another pharmaceutical company, who is outsourcing activities.

Scheduling audits to suppliers and contractors can be based on risk assessment (Rönninger and Malcolm 2009). The time interval between audits can be adjusted based on risk evaluation. Frequency of audits should be increased when the risk factors have been found to be low and vice versa.


Figure 18. FDAs six-system inspection model (FDA guidance 2006)

## 6.5 Internal audit procedure

The audit procedure relies on the audit principles (EN ISO 19011:2002). The audit has to be an independent and systematic process based on evidence in order to be advantageous for the company. Auditor`s independence and competence enables a fresh point of view to be brought out and common principles help auditors to reach similar conclusions about the audited system (Goldberg and Shmilovici 2005). Principles make the audit more reliable and effective and they "guide good auditing practice" (Karapetrovic and Willborne 2000). It would be hard to make any decisions based on unreliable audit results or try to improve QMS based on these decisions.

### 6.5.1 Audit system

Internal audits can be organised freely after company`s own needs but this should always be well documented and a procedure and programme for internal audits should be formed (Pharmaceutical quality group 2001). The audit procedure can be build up like a three-tier system, where audits are managed at three different levels. Audit functions can be determined at system, programme and individual audit level (Figure 19, Karapetrovic and Willborn 2001). The same audit policy applies to all these levels and the policy is determined by the management at the strategic level to make sure that audits can support the overall business goals. In the audit policy, audit process and resources are described. In addition responsibilities and audit principles are determined. Regulatory and business drivers, which set common requirements for the audit, influence the audit policy.

It is important that the audit objective is clear and it is communicated to the people involved in the audit process (Beckmerhagen et al. 2003, Ramly et al. 2008,). Also planning and resources are crucial for a successful audit. According to Ramly et al. a successful audit has to include the following three features. Firstly, audit should be a systematic approach, which takes into account also the follow-up activities resulting from the audit findings (e.g. CAPA, change management). Secondly, the scope of the audit needs to be well defined to cover all the important aspects and being focused on

specific area of interest. This part should also take into consideration the resources and time spent doing the audit itself. Lastly, the auditor needs to have good skills and knowledge to carry out the audit in practise.

When deciding on the annual audit plan or the course of an individual audit, it is important to determine the scope and clearly define, which parts of business should be audited (Kausek 2008). This ensures proactively that the right information of the organisation`s important functions can be gathered and enough resources and time is provided.

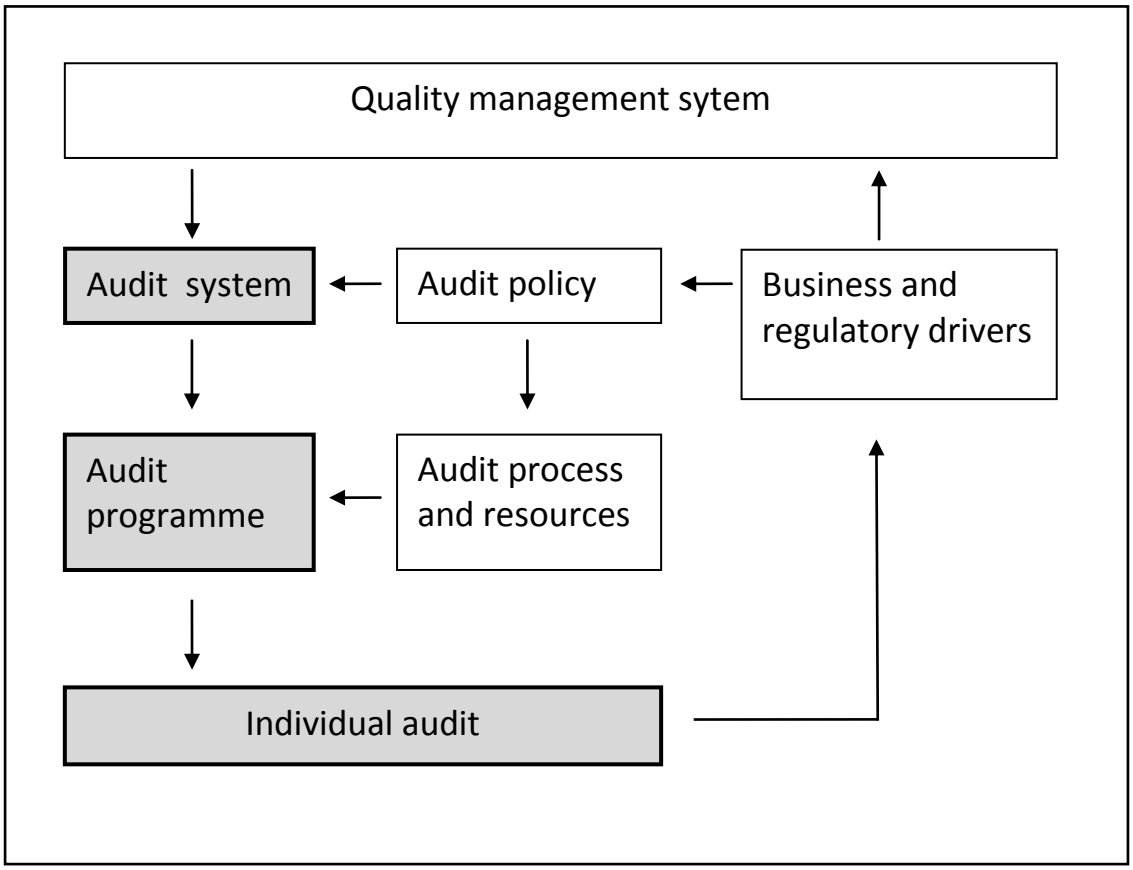


Figure 19. Separate individual audits form the base for the audit program and audit system, which is a part of QMS (Adapted from Karapetrovic and Willborne 2000, Pharmaceutical quality group 2001)

### 6.5.2 Audit programme

Audit is a process in itself and should be well planned, documented, focused and conducted according to audit plan and annual audit schedule (Probitts 2000, Taormina 1999). Audit programme explains in detail the schedule and activities of the audit. The audit schedule needs to cover key elements of the audited system (e.g. QMS) at specified frequency to give comprehensive information about its status. The audit activities need to be established and agreed upon to allow consistent approach to audits (Askey and Dale 1994).

Audit programme consists of individual audits, which have objectives according to policies and principles set by the management (EN ISO 19011:2002). Management has to ensure that necessary resources are provided and responsibilities are shared within the audit programme (Figure 20). Resources should cover financial resources, utilization of audit techniques and finding competent auditors and technical experts. Previous audit results and the opinions of interested parties can be utilized when establishing the extent of the audit programme.

Those responsible of the audit programme should have the competence of auditors and should understand the principles and the techniques of auditing (EN ISO 19011:2002). Establishing the audit programme involves the “planning”- stage of the programme. The main goal is to set objectives for the audit programme. These objectives should take into consideration the priorities of the management and the regulatory and customer requirements. Establishing and monitoring the relevant objectives is essential to be able to meet the set requirements and maintaining confidence to the developed system. Another goal is to establish the extent of the audit programme. This depends on the size, nature and the complexity of audited system. Also the frequency of the conducted audits should be considered. A risk management system could be utilized at this point to reveal any weak points or objectives, which should be audited more carefully (ICH Q9).

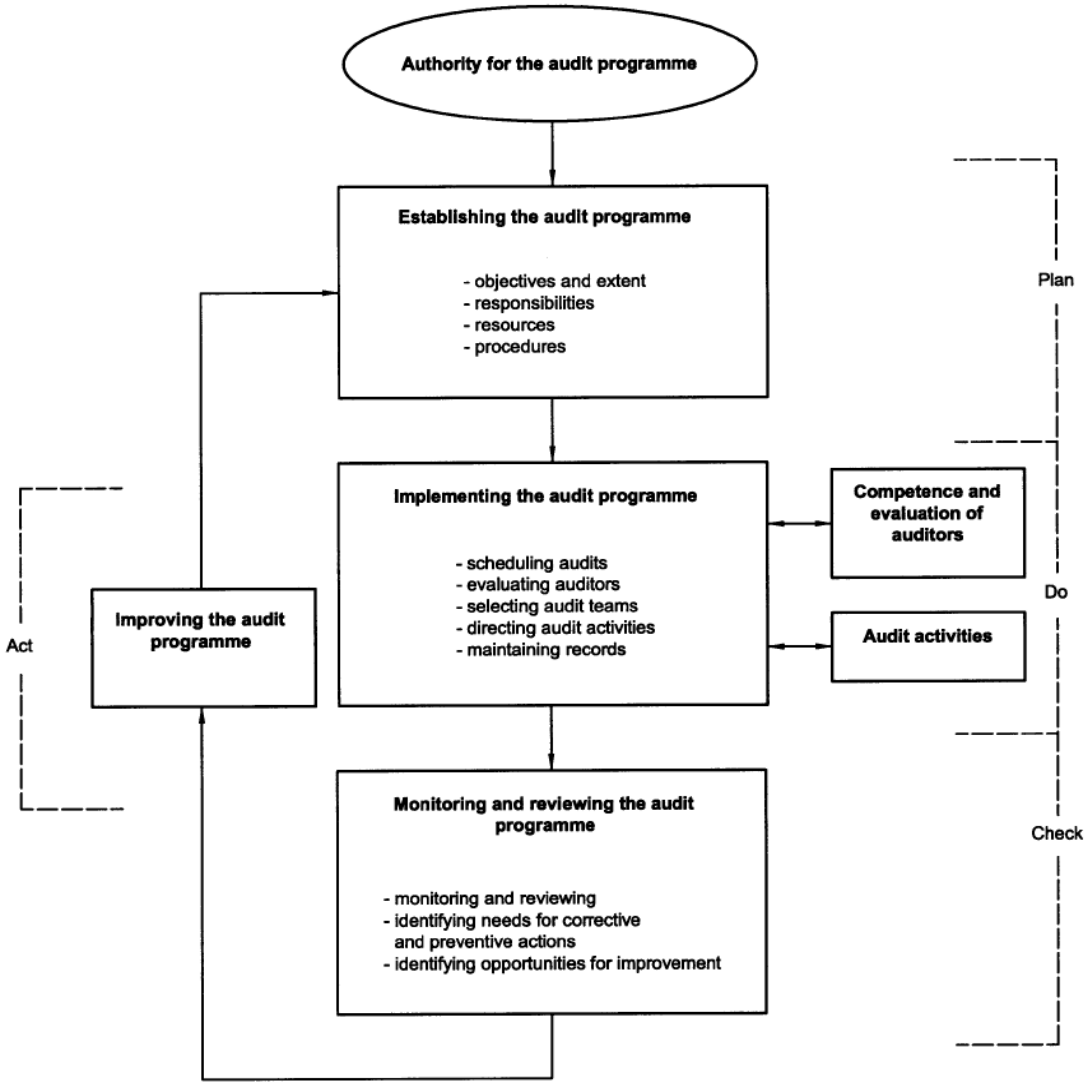


Figure 20. Audit programme (EN ISO 19011:2002)

### 6.5.3 Individual audit

The audit programme is put into practice through individual audits (Figure 21). Audit starts with a preparation phase where, the audit schedule is formed and audit scope objectives and techniques are determined. At this stage it should be ensured that the audit is conducted according to the planned audit programme. Audits should be scheduled in well in advance to benefit those who are being audited (Taormina 1999). As auditees prepare for the audit and go through the audit, they gain information about

their own processes. Elliot et al. have studied auditing from auditor`s and auditee`s point of view and realizes that the biggest disagreement in the audit process concerned the preparation to audit (2007). Both auditees and auditors tend to underestimate each other's efforts to prepare for the audit.

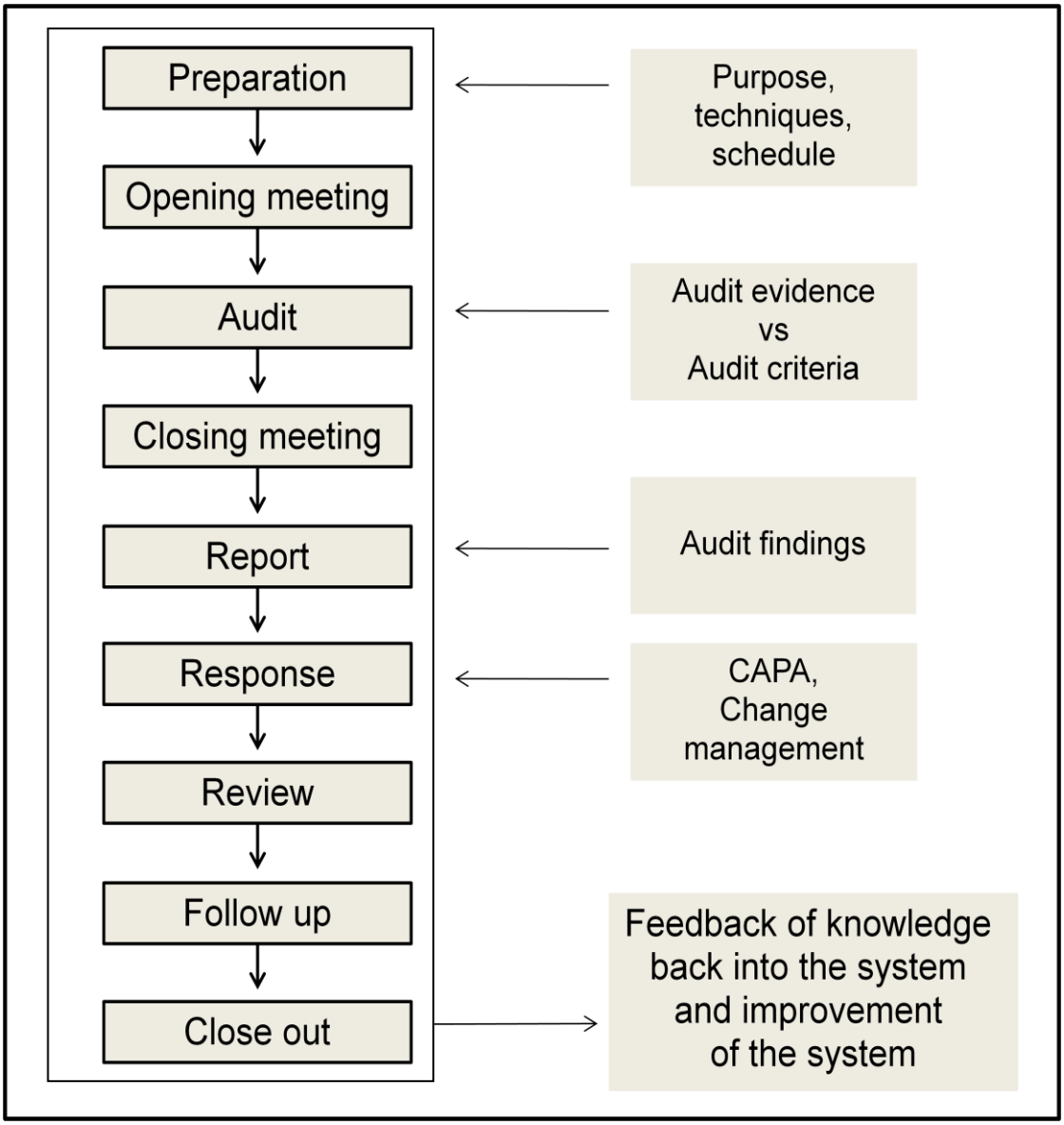


Figure 21. Build-up of an individual audit (Adapted from Pharmaceutical quality group 2001)

Good preparation for the field work is essential for a successful audit. Prior reports and audit programs can be reviewed to determine the scope of the current audit and planning an audit checklist is a part of preparation to an audit (Taormina 1999). The checklist can help guide a consistent audit in a large organization (Probitts 2000). A preliminary survey sent to the auditee can determine the activity objectives (Sawyer et al. 2003). The preliminary survey can also help to identify what kind of information and documentation should be gathered at the site of audit. Based on the survey, auditor can prepare questions to make a formal questionnaire and to find out in more detail about the process. Answering to such a questionnaire is an opportunity for self evaluation for the auditee. Also a pre-audit meeting before the opening meeting might be a good way for both auditors and auditees to prepare for the audit (Askey and Dale 1994). This meeting should be held few days in advance of the official audit. Objectives, purpose and preparation of checklists and other materials (results of last audits) could take place and even a tour of the audited facilities could be arranged. All this preparation makes the official audit run more smoothly and on schedule.

Opening meeting initiates the audit activities on-site (EN ISO 19011:2002). In this meeting audit plan is confirmed and the courses of audit actions are explained. Open communication should be practised effectively during the whole audit and communication channels should be established and agreed about formally.

During the field work information and evidence of the audit activities (audit plans, audit reports, CAPA reports and nonconformity reports) are systematically gathered, recorded and evaluated (Sawyer et al. 2003). Short audits concentrating on detailed areas have shown to cause less disruption and are considered positively among auditees (Askey and Dale 1994). Karapetrovic and Willborn (2001) have created a generic model for auditing, which gives an overview of the audit process and can be applied for different types of management systems (Figure 22).

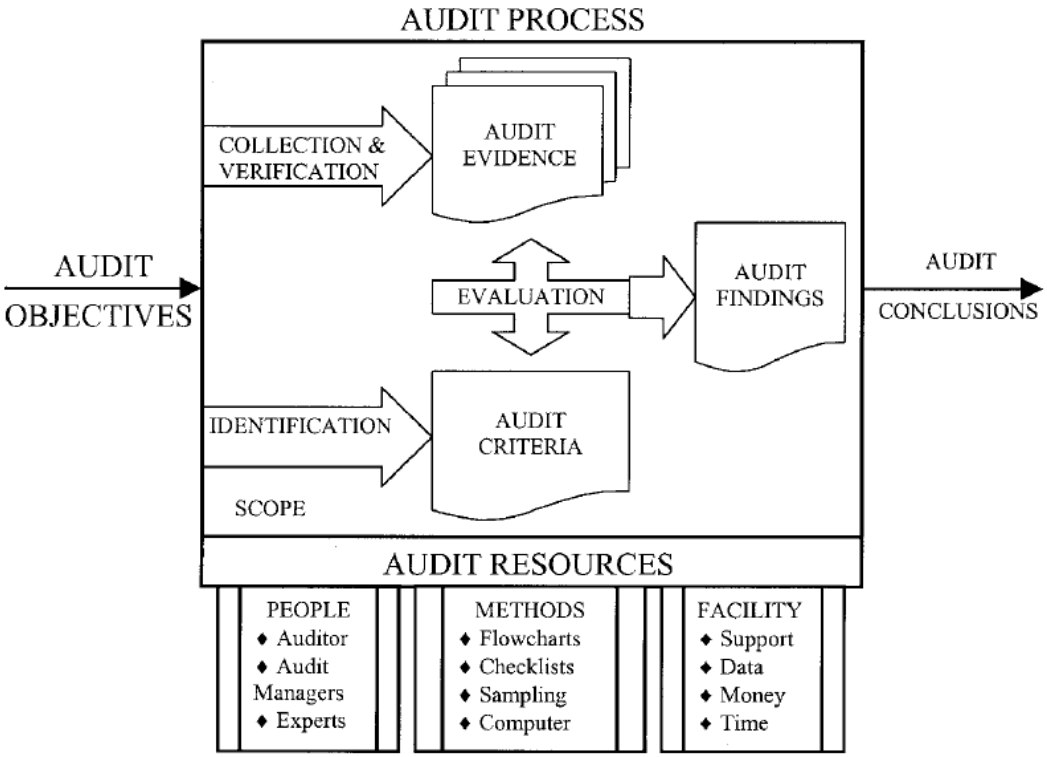


Figure 22. “Generic audit practice” (Karapetrovic and Willborne 2001)

Audit resources are utilised in audit-process to transform the audit objectives through collection of objective audit evidence and comparison with audit criteria to audit findings, from which conclusions about the functionality of audited system can be drawn. The main audit criteria in pharmaceutical industry consist of regulations. GMP guidance is utilised to ensure consistent and controlled manufacture of products (GMP Chapter 1). Other guidance in the pharmaceutical industry consists of ISO standards, ICH Q10, and other relevant documents. This guidance is often quite flexible and is applied according to the size, function and needs of the company. Besides the compliance to guidance, also the proper interpretation and the effective execution of it, needs to be evaluated.

A closing meeting ends the audit activities on-site. In this meeting the audit findings and the conclusion are discussed and suggestions to improve the audited system can be made and corrective actions can be recommended.

Audit results in audit findings and proposed action, which are agreed upon and presented in an audit report at the closing meeting or as soon as possible (Askey and Dale 1994, EN ISO 19011:2002). The audit report is a complete and clear record of the conducted audit and it can communicate, explain and persuade management to take action to improve the audited system. The report often consists of required corrective action and suggested improvements.

A follow-up audit is not necessarily part of the audit itself but it can be conducted if it has been stated in the audit plan or if the audit finding was categorised as a major finding. Minor findings are often checked during the next scheduled audit. If different audits show similar trends also other departments can be checked to see if they had similar problems. This way an organisation wide improvement could be achieved.

Internal audits in pharmaceutical industry are done routinely according to prearranged plans (audit programme) and "for cause" e.g. when recalls and rejections occur, a change has been made to the process, after corrective action has been taken, or prior to external inspection (GMP Ch 9, WHO Annex 4). Corrective measures should be recommended immediately if any deviations are found. Appropriate corrective measures should be done and these should be monitored as well.

### 6.5.4 Audit findings and consequences

Audit findings traditionally consist of the deviations from standard procedures or the risks, auditors find when auditing a process or a system (Sawyer et al. 2003). Findings should be reported clearly and objectively and unnecessary delays should be avoided. Only significant findings relevant to the issue and based on facts should be officially reported. Audit findings are based on observations, background information and previous audit reports.

Auditors can also report weaknesses, best practices and improvement suggestions they identify during audits and they may emphasize the importance of these findings concerning the current interests of the organisation (e.g. effectiveness of QMS) (Kausek

2008, Morris 2008). Audit findings can be classified as major findings, multiple minor findings, which lead to a major finding, or minor findings (Taormina 1999). Also observations, which are deviations or risks observed during audit, but are out of the scope of the present audit, may be reported. They can form a foundation for a new audit.

Audit results are presented to management in the form of audit reports and management review. This makes management aware of current state of activities and focuses management`s attention on possible improvement ideas and might lead to allocation of resources and even re-evaluation of existing strategies (Kousek 2008).

CAPA activities are done as a response to audit findings to fix the underlying problem and prevent its recurrence (Taormina 1999). Auditee should investigate the root cause of the deficiency and take action to prevent it in the future. This action may include changes to the process or training of the employees. Follow-up to ensure the efficiency of the corrective action can be done during the next periodic audit. CAPA and training of the employees should be used as a tool to improve the QMS.

It is important to remember that the audit process does not end with the audit report (Beckmerhagen et al. 2004). Action needs to be taken to fulfil the wanted outcome of the audit process based on the evaluation of the findings. Audit report is a way to drive improvement of both the audited system and the audit process itself (Morris 2008, Figure 23). This is done by saving the records of how the audit was conducted and gathering information about audit findings to plan and improve the future audits.

Audit report contributes as an input to management review and CAPA system. The management of the audited field receives the audit report and can make decisions based on it. This way people working in the audited field may start improving the audited system/process based on internal audit results (e.g. via CAPA and change management system) and contribute to improve system/process. The responsibilities of these actions are also shown in Figure 23. Although the on-site activities demand full attention from both auditor (QA) and the auditee (audited department), the responsibility of further

action goes to either QA or the department depending on what is focused on (improvement of audit process or improvement of the audited field).

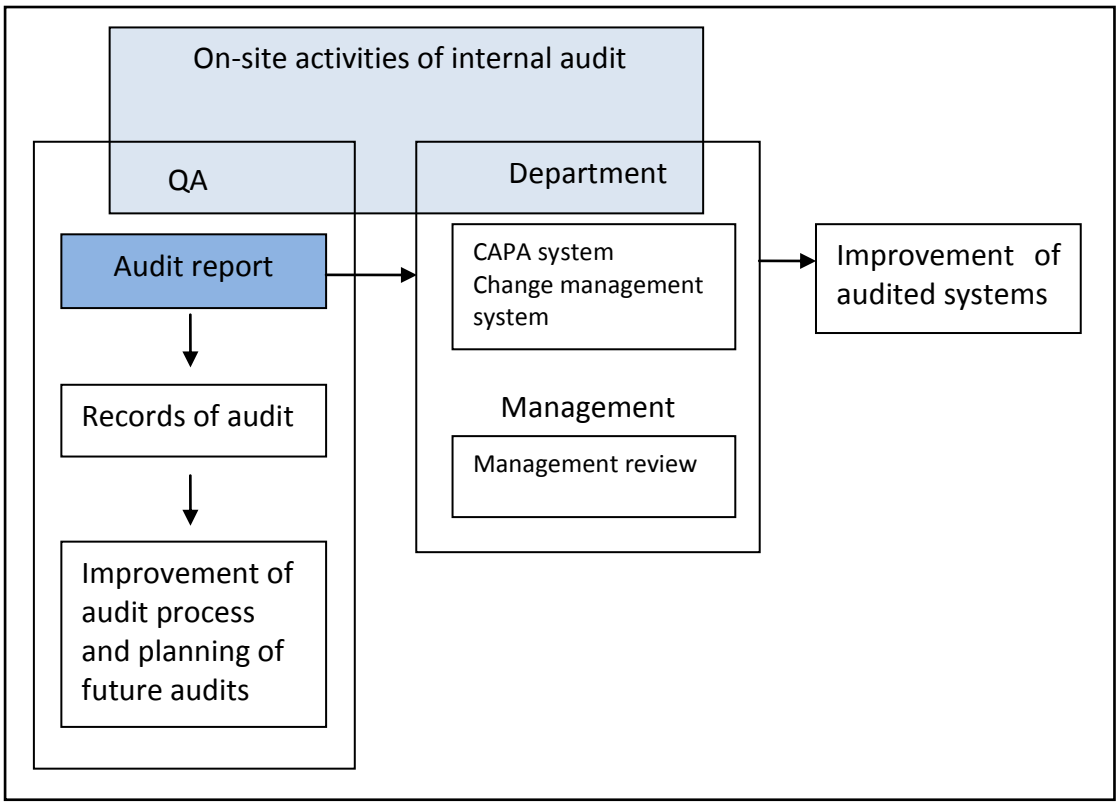


Figure 23. Utilisation of audit report (adapted from Beckmerhagen et al. 2004 and Morris 2008).

## 6.6 Auditors

Audits can be conducted by an independent organization within the company or by external experts (GMP Ch 9). In pharmaceutical industry this independent organization is usually the QA-organization. Internal auditors have a dual role (Fadzil et al. 2005). They need to assist organisations management, but at the same time they need to critique and challenge the existing procedures. Also good administration of audit is needed so that the auditors can concentrate on the audit itself (Askey and Dale 1994). Auditors may need support with preparation, assembly of documentation, scheduling meetings, taking notes, help with the report, follow-up, presentation of results and training.

### 6.6.1 Auditor skills

Auditors should conduct the audit in an ethical manner (EN ISO 190011:2002). This should be the foundation of professionalism of all the audits. Auditor should give a fair, truthful and accurate presentation of the findings of an audit. Auditors have to be competent experts in the field they are auditing and master internal audit techniques (Sawyer et al. 2003). Internal auditors evaluate information and make recommendations based on the findings (EN ISO 190011:2002). Expert knowledge is needed in plotting the risk factors behind the system and finding cause and effect relations. In addition, an audit has to remain as an independently and non-partially functioning system in order to be objective. When all the audit conclusions are based on evidence, reproducible audits can be conducted and conflict of interest and bias is avoided.

Management need to make auditors aware of the importance of organisational goals and strategies so that auditors are able to link the audit of processes, products and systems to the wider strategy of the organisation (Kousek 2008). Auditors have the ideal position to identify these connections.

### 6.6.2 Audit teams

Audit teams can be more efficient than auditors working by themselves (Askey and Dale 1994, Taormina 1999). Results can be compared when working in a team and tasks can be more effectively shared e.g. observation, interviewing, and taking notes. This leads to a more objective audit with a deeper knowledge gained about the audited process. If company`s resources are not sufficient to carry out own audits, shared audits, mutual recognition agreements or outsourcing of audit activities can be considered (Skubch and Zimmer 2009).

Although internal audits should be conducted by auditors independent of the process, there have been positive cases of auditing, where the senior managers of the audited process participated on the auditor-side (Askey and Dale 1994). Managers gained more knowledge of their own systems and the corrective actions and improvements, which

resulted from the audit, were more willingly done. Also the overall motivation to improve the performance was increased. This untraditional approach could even be taken further by including the employees, who work with the processes in the operational level, to participate in the audits. Switching roles in this manner can enable people to consider their own operations from a new perspective.

## 6.7 Audit techniques and tools

Different techniques and tools are used to generate audit findings (Sawyer et al. 2003, Taormina 1999). The main focus is on collecting data and evaluating it to create meaningful information (Chan et al. 1993). The value of accurate and easily accessible information gathered and created in internal audits is emphasized as "the quality of an audit depends on the usefulness of its results to management". Review of documentation is done to find out about the procedures at the site. Interviews are conducted to see if employees are trained accordingly to their job prescription and whether they follow the written procedures. To confirm these results, observations of the process is important. The style of the audit depends on the audit objectives (Probitts 2000).

### 6.7.1 Review of documentation

Appropriate sampling should be applied when collecting information from different sources during audit (EN ISO 19011:2002). The collected information should be relevant to the objectives of the audit and only verified information should be used. The review of documents concerning policies and procedures helps to assess compliance (Sawyer et al. 2003). Flowcharts of the operations can clarify the process flow and help identify weaknesses of the system. Also the accessibility and employees knowledge about documentation and records provides an important observation for the auditor (Askey and Dale 1994).

### 6.7.2 Observation

Throughout the whole audit, the auditor is observing the facilities and the people working on-site (Sawyer et al. 2003). This helps the auditor to determine the objectives of the audit activities, to evaluate risks and to identify controls. It is important to understand that the auditor`s presence might affect employees work and take this in to consideration as observed work is compared with procedures (Askey and Dale 1994). Tour of the facilities should be made to gain understanding of the location, condition and layout. A more thorough observation can be made by observing a significant process in detail from start to finish and assess its compliance. If the observation of work is not giving auditor the wanted information, auditor can interview the employees about what they would do in hypothetical situations (e.g. abnormal procedures).

### 6.7.3 Interview and questionnaires

In order to obtain deeper insight into the processes, interviews need to be carried out. Auditors should have good interview and communication skills to encourage dialogue (Sawyer et al. 2003). Questions should be prepared in forehand to meet the objectives of the audit. Audit interviews should be scheduled and done one-on-one at the audited location. Interviews of employees are done to see if procedures are being followed (Taormina 1999). Generic, open-ended questions derived from quality manual procedures or SOP`s should be asked to get objective and unbiased answers (Morris 2008). It is understood that one cannot simply answer yes or no to an open question. This type of question setting enables the interviewee to answer with his/her own words. Follow-up questions and related questions can be asked to clarify the information and to avoid misapprehensions. The best way is to let the auditee describe situations with own words as this usually results in more valuable and comprehensive information. The more traditional way is to use checklists based on the requirements of the audited process. This might be a good aid as time has to be managed while auditing, but the checklist questions must not be leading or consist of closed questions only.

It is important to include the right persons to participate in the interviews (Morris 2008). Process owner and other employees with first-hand knowledge about the operations can provide the auditor with most valuable information and auditor can form an idea of the effectiveness of the system based on this information. In return the process owners involved in the audit are in the forefront to gain knowledge about their own systems. Interviews should not follow checklists or questionnaires too strictly to allow the discussion of possible scenarios, development ideas and even out of the box thinking.

### 6.7.4 Analytical methods

Analytical methods can help identify risks (Sawyer et al. 2003). These methods are flowcharting, internal control questionnaires, and matrix analysis. Flowcharts can help in the analysis of efficiency and control in a process. These graphically present the process of an operation. Getting information about a process can be achieved in the form of a questionnaire with open and closed questions. Analytical and quantitative methods can be used to analyze audit findings and support decision making. Mathematical and statistical models can be descriptive or predictive. Trend analysis is a quantitative technique, which horizontally analyses change. Ratio analysis evaluates variation and can compare different results. Also regression analysis is used where relationships of variables are analyzed.

## 6.8 Effective audit

Audit needs to be effective to gain the full benefit from it (Ramly et al. 2008). It is effective when it is adaptable to the external changes, which effect the audited environment. These external changes could be due to novel technology or new guidelines. If the audit system (or quality system) is too rigidly structured, it might prohibit the inspection of the most important parts, namely the parts which are susceptible for change. Audits should fulfil the set goals as planned with reasonable resources (Beckmerhagen et al. 2004, Morris 2008). The goal of the audit should be clear e.g. whether the goal is to conduct compliance audits or audits aimed to improve processes. When the goal for the process is set, it should be measured to see if and how

this aim is met. It is also important to figure out strengths and weaknesses of the whole audit process including audit plan, process and resources. Audits effectiveness can be assessed by focusing on the reliability and possible risks of audit. Improvements can be done to keep the audit running smoothly and gaining the most of it.

How effectively audits are conducted can be measured by establishing a system to record the number and nature of discovered defaults and compare these results to previous audits. Ideally same type of problems should be reduced over time (Elliot et al. 2007). Also measurement of the audited process` performance can be done based on number and nature of nonconformities recorded in audits (Askey and Dale 1994).

Doing the audit more effectively also adds value of the audit as resources are utilised more efficiently. There are several different criteria, which can contribute to an effective audit (Table 6). As can be seen from the table, effective audit consist of audit planning, conduction of audit, audit findings and action taken because of audit. Therefore measurement of the effectiveness of audit cannot be based merely on the number of audit findings, but it could also be based other criteria, such as the ones shown in Table 6. By sending surveys or interviewing people involved in the audit process, valuable information and measures about the audits effectiveness can be gained (Beckmerhagen et al. 2004, Rajendran and Devadasan 2005).

Table 6. List of criteria for effective audit (Adapted from Beckmerhagen et al. 2004)

| **List of criteria for effective audit** | |
|---|---|
| 1 | Approved and defined audit objectives |
| 2 | Suitable audit plan |
| 3 | Adequate resources and time to conduct the audit |
| 4 | Conducting the audit according to plan |
| 5 | Audit results in objective and valid audit findings |
| 6 | Audit findings are analysed against set objectives |
| 7 | Audit findings must lead to corrections and improvements |
| 8 | Audit findings are communicated to interested parties |
| 9 | Audit provides evidence about the improvement of the QMS |

Besides measuring audit effectiveness, it is important to gain reliable audit findings and minimize the probability of audit failures (Beckmerhagen et al. 2004). Limited time to conduct the audit, gather the evidence and make the assessment of performance of systems make the audit process challenging (Morris 2008). Audit failures are often due to poor skills of the auditor, preparation and timekeeping (Askey and Dale 1994, Karapetrovic and Willborn 2000, Ramly et al. 2008). Also lack of commitment from management, auditor and auditee side and lack of resources and action to the results of the audit can undermine the whole process of auditing.

To find out whether or not the objectives and criteria of the audit have been met, the audit programme should be monitored, reviewed and improved in a timely manner (EN ISO 19011:2002, Karapetrovic 2000). This is the audit of the internal audit. Results of this review should be reported to the management (management review of quality systems/ICH Q10). Continual improvement of the audit programme is based on the findings of the monitoring and evaluation of met audit objectives. If audit programme is not easy to follow, there might be deviations from it and this can lead to inconsistent and unreliable results.

## 6.9 Utilisation of internal audits

Audits are performed to ensure the efficacy of the process and the quality of the product (Schindel-Bidinelli 1996). With the help of audits, also the compliance with and effectiveness of processes and quality system can be determined. These different audit objectives can be reached with different types of audits (as discussed in Chapter 6.4). Audits serve both top management and the employees (Karapetrovic and Willborn 2001). Audits can be beneficial for the whole organisation at all levels of hierarchy if audits are done effectively and utilised more fully in various ways. Next, different ways to utilise audits are looked at more closely.

### 6.9.1 Audit as a mean of controlling a process

Organization activities exist on two levels; operational and control (Sawyer et al. 2003). Production of a product according to set standards happens in the operational level while the procedures, which make sure those standards are met, are in the control level. Internal auditors should concentrate to evaluate the control system rather than the product (Goldberg and Shmilovici 2005). The effectiveness and efficacy of controls should also be evaluated and improvements to control system should be suggested.

A process is defined as a "set of interrelated activities which transforms inputs to outputs" (EN ISO 9000:2005). Since the process is a series of activities, one activity can have a big impact on another. Process controls are developed to design a control strategy, which improves the robustness and consistency of the system (McConnel et al 2010, ICH Q 8). Controls can help prevent, detect or correct different outcomes and thus they can determine the quality of the product (Sawyer et al. 2003). Feedback and control make sure that the process is producing products according to set standards continuously (Figure 24).

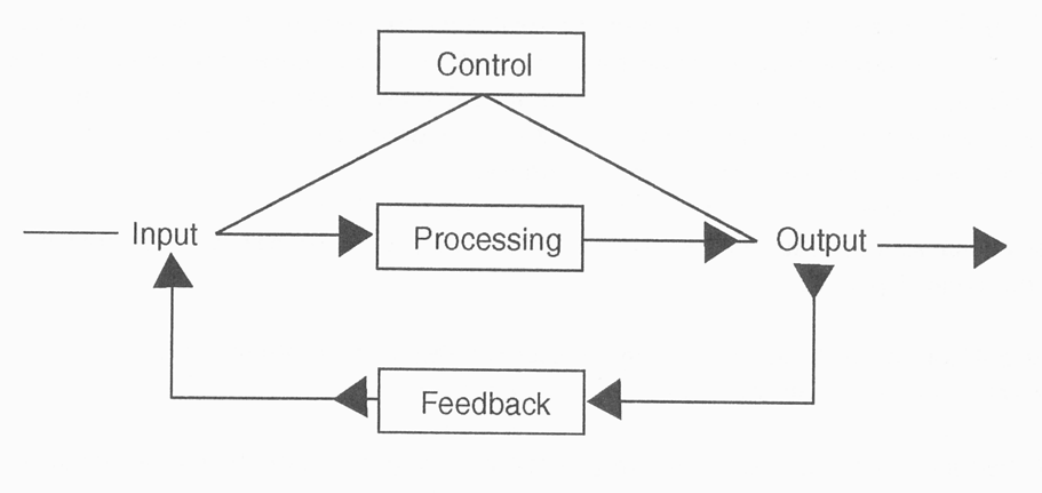


Figure 24: Control and feedback helps to keep the process under control (Sawyer et al. 2003).

Control is a way to compare real outcomes with the planned outcomes (Sawyer et al. 2003). Controls should be flexible enough to allow certain changes to be made to improve the system within reasonable limits. Appropriate amount of controls is cost

effective and does not waste resources on trivial issues. Controls are audited by analysing the controls and assessing the risks and objectives associated with the process.

### 6.9.2 Audit as a mean of improving the audited system or a process

Besides defining current status of performance and compliance, audits can be utilized to implement change and improvement (Karapetrovic and Willborn 2001, Rajendan and Devadasan 2005, Ramly et al 2008). Audits are used to both, identify areas for improvement and plan improvement actions. Ultimately this can lead to improved performance through improvement of product quality and reduced manufacturing costs.

Crombie and Davies (1993) recognized improvement as a difficult task in the field of health care and suggested a fundamental step to the audit cycle, namely finding the underlying cause for the failure (Figure 25). The same issues have been acknowledged by Elliott et al. (2007) who found out that particularly the analysis of problems and realisation of improvements have been seen as the most problematic and ineffective part of auditing.

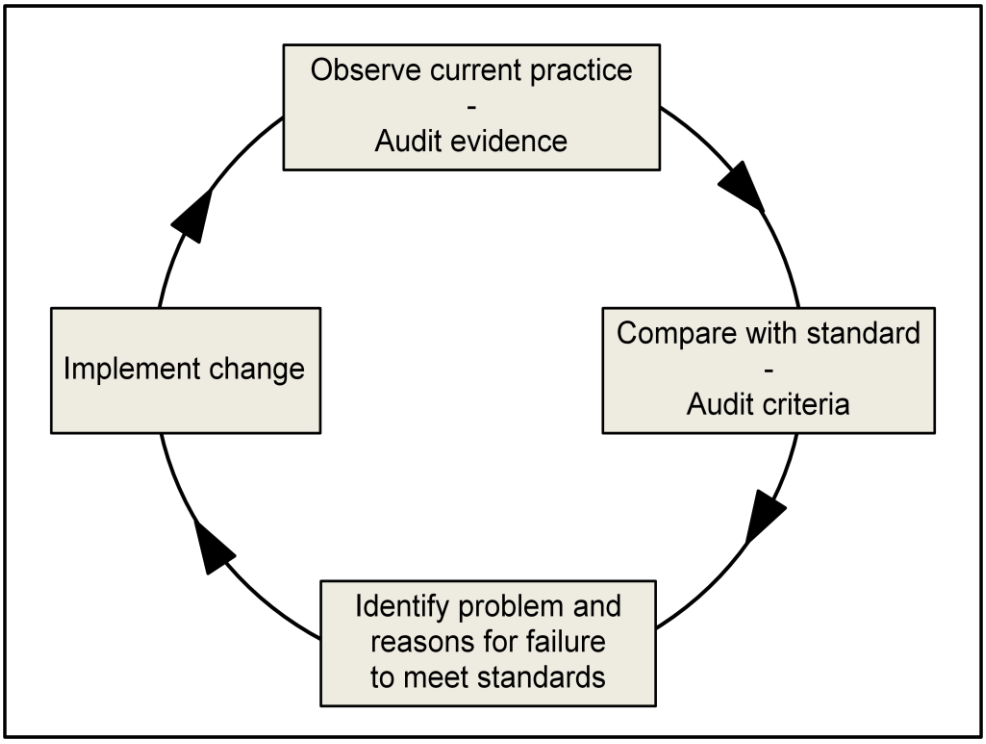


Figure 25. Audits as a means to implement change (Adjusted from Crombie and Davies 1993)

The strategy for change has to involve a step committed to identifying the problem and reasons for it. In pharmaceutical industry CAPA-systems are used at this stage to identify areas for improvement (Percy 2010). Internal audits should be integrated with the CAPA systems and change management, to gain efficient and continuous improvements. Without a thorough investigation of the problem, audit only results in a list of defects with no clear indication how to solve them. Auditing should fix poor practice by revealing the root cause of a problem and by improving the system. Also the effect of the change should be evaluated. This evaluation can be made in the form of risk assessment before initiating the change and by repeating the cycle again to ensure the promotion of continuous improvement in the future.

### 6.9.3 Audit as a mean of assessing the functionality of a QMS

The effectiveness of a QMS can be evaluated with a quality assurance/system audit (Goldberg and Shmilovici 2005). It measures whether the quality objectives are met and can identify the need for improvements. In the pharmaceutical field, compliance to GMP objectives can be audited by QA (Figure 26, GMP Chapter 1). Feedback loop from CAPA and management reviews is necessary to continuously improve processes and systems (Edwards 2008). This way an assessment of the functionality of the QMS can be done.

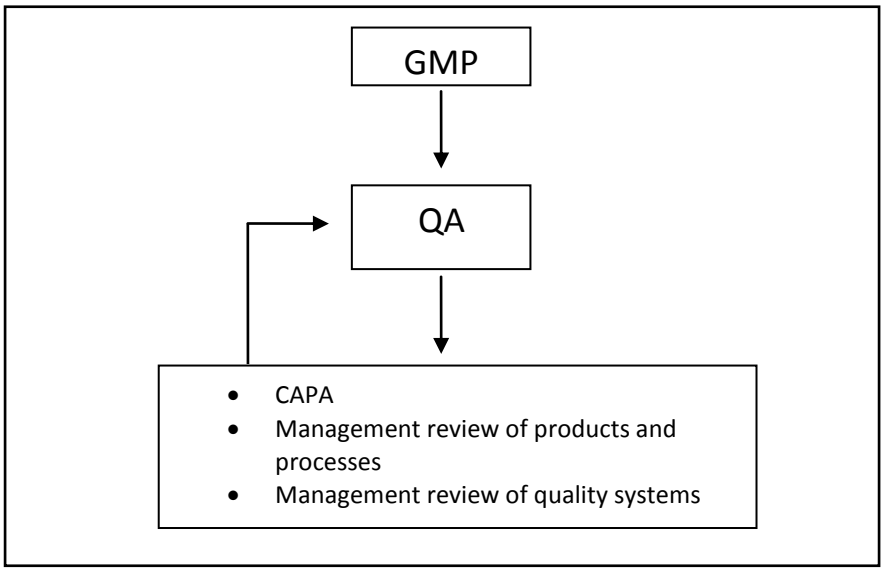


Figure 26. Assessment of the functionality of QMS

### 6.9.4 Audit supports management`s decision making and serves as a learning opportunity

Internal audits provide an important source of information and this eases the decision making for management (Chan et al. 1993). The whole organisation benefits from this, as status of meeting organisational goals is reached and new objectives can be set based on this valuable information. Internal audit can thus help in achieving organisational goals and execute the organisation`s strategy (Kausek 2008). Audit is a learning experience for the organisation. It is important that the organisation learns from the audits and understand the true cause behind the finding.

### 6.9.5 Preparing for a regulatory inspection

Critical deficiencies should be identified and corrected by the company's own internal audit (self-inspection) programme before a regulatory inspection takes place (Poska 2010). It is important to prepare for such inspection by evaluating manufacturing processes, protocols and activities (Rodriguez 2005, Drakulich 2008). The functionality of the most critical areas of QMS and its compliance with GMP should also be evaluated, because regulatory authorities will inspect QMS as part of a regular GMP inspection. These preparatory audits can mimic the regulatory inspection done by authorities to recreate the readiness of the company for such an inspection (Probitts 2000).

Reduced regulatory oversight in the form of reduced inspections can be gained by demonstrating the effectiveness of the company`s self inspection programme (Poska 2010). Regulatory authorities seldom request to see internal audit reports. Some companies would be willing to consider a more open approach and share some of their internal audit reports with the authorities, if a less frequent and less intensive regulatory inspection could be achieved (Jeronic 2010).

### 6.9.6 Risk based approach to internal audits

Internal audit programmes can be put to use with quality risk management principles (ICH Q9, Jeronic 2010, Skubch and Zimmer 2009). This kind of approach can be used to assess potential risks of quality and to focus internal audit activities to areas with higher risks. Planning and conduct of internal audit and response to internal audit findings can include risk management concepts. The frequency and scope of inspection can be planned so it's commensurate with the risks involved. In this way resources are more efficiently used.

A survey study has been conducted to find out whether and how quality risk management has been applied to self inspection programmes in pharmaceutical companies in Ireland (Jeronic 2010). According to the survey, internal audit (self-inspection) was found to be part of risk management in 31% of the companies. In 50% of the companies self inspection was used as an independent part of quality system to just monitor compliance and SOPs. In the rest of the companies the use of self inspections was something in between these two types. The survey also determined the extent of applying risk management to different aspects of the QMS and the tools used for this. Nearly half (44%) of the companies used some form of risk management tools to assist in internal audits (Figure 27).

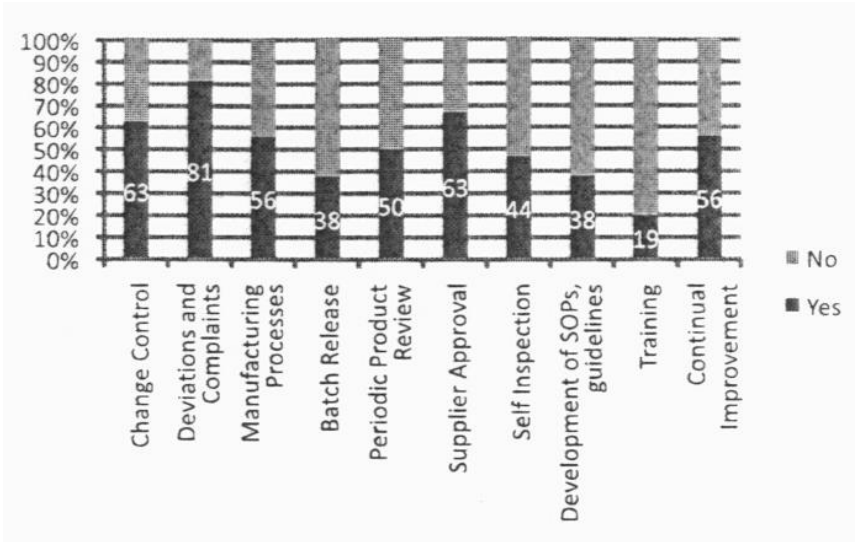


Figure 27. Risk-based approach to internal audits and other functions (Jeronic 2010)

FMEA, process mapping, cause and effect analysis, HAZOP and flow charts were among the most used risk management tools (Jeronic 2010). Planning the frequency and scope of self inspections was done based mainly on the results from previous self inspections and regulatory inspections. Previous quality defects, complexity of the process and changes made to the process were also taken in to account when selecting areas for inspection.

Benefits of a risk based approach are manifold. Proactive assurance of the quality and quality objectives can be achieved with this approach. The ability to prepare and deal with risks, decision making, and use of resources is also improved (ICH Q9, Jeronic 2010).

### 6.9.7 Finding out the best practices

Appreciative audit uses an opposite approach to the traditional audit (conformance to requirements) (Morris 2008). It concentrates on recognising what works and what is correct. It also encourages the auditees to take a more active role in identifying improvement opportunities, solutions to problems and implementing change. Internal audits can become more effective and valuable to the organisation by emphasising on the best practices. More improvement ideas were found and implemented based on the audit findings as top-management got interested in the audit report`s improvement suggestions. The description of strengths and improvement plans were even incorporated in to the organisations strategic plan.

This appreciative method should be used together with the traditional type of auditing to gain a balanced picture of the company`s functions. By getting information on the best practices and non-conformities the organisation activities can be redirected to gain the set goals.

# 7 THE AIM AND PURPOSE OF THE STUDY

This is a qualitative study relating to internal audits and QMS. The aim of this study is to examine the utilisation of internal audits in Orion (Espoo). The focus will be on how internal audits can monitor and guide QMS. The purpose is also to find solutions to improve the utilisation of internal audits and to identify which kind of benefits internal audits may have. How internal audits could be utilised more efficiently is also evaluated. This study can provide supporting knowledge for controlling (monitoring and guiding) QMS with the help of internal audits, and gaining information about better utilisation of internal audits.

The proposition of the research is that internal audits can monitor and guide quality systems. How internal audits can achieve this is also further studied in this research.

# 8 INTRODUCTION TO STUDY METHODS USED IN THIS STUDY

Qualitative research methods used in this study include semi-standardized open-ended interview as an approach to collect information and qualitative methods for analysing the data. Interview as data collection method is a suitable approach for qualitative research where thoughts and viewpoints of the employees are studied. Correctives and reasons for a certain view can be investigated more flexibly with an interview compared to a survey (Hämeen-Anttila and Katajavuori 2008).

Qualitative inductive content analysis formed the foundation for data analysis, which was conducted based on the basic principles of phenomenology and hermeneutics. In addition, some of the techniques from framework analysis and grounded theory were also utilised in this analysis to some extent.

In this chapter, an introduction is given to the study methods used in this work and in the next chapter detailed information concerning this work is given.

## 8.1 Comparison of qualitative and quantitative methods

Different models for research methods have been developed. Common to all these methods is that these aim to view the reality (Silverman 2007). Research methods can be harshly divided in to qualitative and quantitative methods. These two methods are compared in Table 7. A quantitative study, for instance, could be a survey which can reach large population (randomized sample), is statistically analysed and can create generalized conclusions. Qualitative research methods, such as interview, have a smaller scope but handle the information in more detail resulting in deeper understanding of the phenomena. Qualitative and quantitative methods are often thought as exclusionary or contrary, but these methods can also be combined or used at different stages of the research (e.g. data collection and data analysis).

In traditional quantitative research scientific methods are used to gain true knowledge (Kvale 1996). From conventional point of view any influence by the researcher is

considered harmful to the research and may threaten the objectivity of the study. In qualitative research, the researcher has a more central role compared to quantitative research and this may influence the objectivity of the research. The data collection and interpretation of data relies on the competence and the decision-making skills of the researcher. Without a transparent and detailed description of the method of analysis, different researchers could make varied interpretations and produce different findings (Thomas 2003).

Table 7. Comparison of quantitative and qualitative study methods* (Compiled from different sources: Silvermann 2007, Kvale 1996, Zhang and Wildemuth, Lincoln and Guba 1985).

| Study method | Quantitative | Qualitative |
|---|---|---|
| Sample | randomised | purposive |
| Sample size | large | small |
| Data collection | e.g. survey, experimental studies | e.g. interview, observation |
| "Philosophy behind the concept" | positivism | several |
| Researchers role | objective | may influence the research |
| Data analysis | statistical | "general inductive approach", content analysis, grounded theory, framework analysis, phenomenology etc... |
| Output | generalized conclusions | deeper information about the studied phenomena |
| Quality of the study | validity, reliability, objectivity | Trustworthiness: credibility, transferability, dependability, confirmability |

*This is not an exhaustive list. This list shows and intensifies the differences between the features of quantitative and qualitative methods. Some quantitative studies may have some qualitative features and vice versa.

## 8.2 Qualitative research methods

Qualitative research methods are widely used in health (nursing) and social science studies (Thomas 2003). The basis for qualitative research is inductive reasoning, which links different perceptions together from the collected research data (Kvale 1996, Kylmä and Juvakka 2007, Zhang and Wildemuth 2009). The term inductive refers to the approach that findings emerge from the raw data by themselves as opposed to deductively where hypothesis or theories are used to draw information from raw data purposely to get certain information specifically related to the hypothesis or theory.

The objective of qualitative research is to describe reality and understand it from the study-participants` subjective point of view. Qualitative research aims to create new information and theories by analyzing these conceptions of reality. Qualitative research method is often chosen when only little information on the studied phenomena is available or a new perspective on a matter is studied.

### 8.2.1 Sampling

Purposive sampling method is widely used in qualitative research and the sample is often quite small compared to sample size used in quantitative research methods (Kvale 1996, Kylmä and Juvakka 2007). Saturation of data is used to describe the valid amount of data collected rather than the sample size.

### 8.2.2 Interview as data collection method

Data, concerning qualitative research, is collected with open methods such as interviews and observations (Kvale 1996, Kylmä and Juvakka 2007). The collected data is always bound to the context and these methods do not aim to generalize the findings. Interview can be used as a method for gathering qualitative information, because it provides in-depth information from the viewpoints of the interviewees (Turner 2010). There are several different formats for interview design to choose from. Examples of these are informal conversational interview, general interview guide approach and standardized open-ended interview (Gall et al. 2003).

Informal conversational interview is an unstructured interview where questions are spontaneously formed as the interviewer interacts with the interviewee. It is a flexible way to collect data. This method can create inconsistent data and the analysis and coding of the data can be tricky. General interview guide approach is also a flexible approach, but it is more structured compared to the first method. Questions are asked without a strict focus on the wording of the questions. Same themes are covered in each interview. The risk with this method is that questions are not understood the same way in the interviews and this can make it difficult to analyse the data. If the interview is too

standardized or structured and the questions are not open-ended, it starts to resemble a questionnaire, which is used in quantitative research. Semi-standardized open-ended interview is the most popular format for an interview design in qualitative research and it can be looked at as a combination unstructured and standardized approach (DiCicco-Bloom and Crabtree 2006). All the interviewees are asked the same open-ended questions. Follow-up questions are used to get all the necessary information. Coding and analysis can still be challenging due to wide variety in answers, though the content is more uniform compared to the previously mentioned formats.

## 8.3 Data analysis and models of qualitative research

Qualitative research such as interview can produce systematized knowledge (Kvale 1996). There does not exist a single agreed model for a research method within qualitative research, such as positivism in quantitative research (Silverman 2007). Qualitative research models are a variety of different types of approaches and these lay the framework to analyse the qualitative information.

There are different approaches to the analysis of meaning, such as condensation of meaning, categorization of meaning, narrative structuring of meaning, interpretation of meaning and ad hoc approach to meaning (Kvale 1996). A suitable method is chosen according to the purpose and the type of the interview. Question development, the interviews and the transcribing process lay the foundation for the analysis of meaning of the contents of the qualitative information.

### 8.3.1 General inductive approach

The general inductive approach for qualitative data analysis is defined as “a systematic procedure for analysing qualitative data where the analysis is guided by specific objectives” (Thomas 2003). It has been developed and described on the basis of reported study methods where qualitative data analysis had been used. The outline of a general inductive approach can be divided in to three main parts, which aim to analyse the meaning in the raw data (Figure 28). First, the objective is to reduce the amount of

data by condensing the raw text data e.g. by coding the text to create categories and to form a short summary. Secondly, links are formed between findings from the raw data and the objective of the research and lastly, model or a theory from the basis of the raw data can be developed. This general approach has some elements of other qualitative methods like the grounded theory and content analysis (described later in this chapter), but these elements are described more simply and in less technical way in general approach.

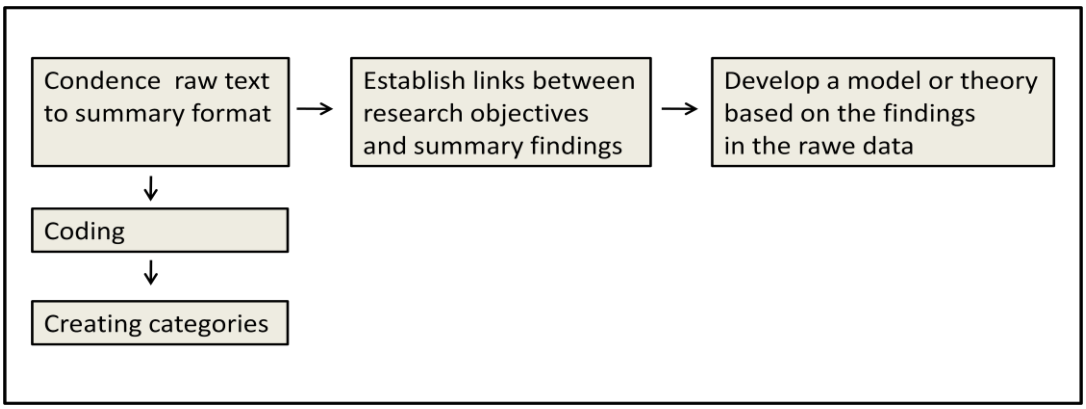


Figure 28. The outline of a general inductive approach (Thomas 2003).

Inductive coding resulting in category creation and revision is the core of the analysis. The findings are the emerged categories. According to Thomas, "most inductive studies report between three and eight main categories in findings" (2003). If there are more categories, the analysis is considered incomplete. This is why categories may have to be compiled to create larger entities of categories or the researcher may have to consider the importance of findings (categories) and leave some less important findings out.

### 8.3.2 Content analysis

Originally content analysis has been used to interpret historical texts (hermeneutics) to find the meaning behind the message or analyse texts in a quantitative way by counting textual elements (mass communications) (Mayring 2000, Zhang and Wildemuth 2009). It is used today to analyse all kinds of recorded material such as transcribed interviews and videotapes by both quantitative and qualitative approach. These two approaches are often combined in a following way: quantitative analysis, where the frequencies of

comments or coded categories are counted, supports the main qualitative content analysis. Quantitative content analysis alone is often insufficient as analysis of qualitative data. Qualitative content analysis can also be incorporated with other qualitative approaches, which are described later in this chapter.

Qualitative content analysis is defined by Mayring (2000) as "an approach of empirical, methodological controlled analysis of texts within their context of communication, following content analytical rules and step by step models, without rash quantification". According to this definition qualitative content analysis can be looked as a scientific method to gain information about a phenomenon in a non-generalized way (subjective). Hsieh and Shannon (2005) have considered the role of inductive reasoning in qualitative content analysis and according to that they have discussed the following three approaches. Namely, conventional content analysis, directed content analysis and summative content analysis. The conventional content analysis is inductive in nature as the coding and categories emerge from the data. Directed content analysis starts by deductively coding the text, but the formed categories are further analysed inductively (findings emerge from the formed categories). The summative content analysis consists of counting of words and interpretation of these words. Table 8 illustrates the differences between these approaches.

Table 8. Differences in coding process between the three approaches to qualitative content analysis (Adapted from Hsieh and Shannon 2005).

| **Approach to content analysis** | **Conventional content analysis** | **Directed content analysis** | **Summative content analysis** |
|---|---|---|---|
| Role of inductive reasoning | Inductive | Deductive and inductive | Deductive (counting)<br>Inductive (interpretation) |
| Other similar methods | Grounded theory, phenomenology | Framework analysis | Quantitative content analysis |
| Timing of coding | During data analysis | Before and during data analysis | Before and during data analysis |
| Source of codes | Derived from data | Derived from theory and research findings | Review of literature/<br>Interests of researchers |
| Output of the analysis | Concept development, model building | Supporting or extending a theory, validate theory or hypothesis | How words are used and meaning of the words |

### 8.3.3 Phenomenology

Phenomenology is the study of consciousness and experiences (Kvale 1996). In an interview research phenomena is described from the interviewee`s perspective as he or she experiences it in relation to their perception of reality. Phenomenology creates the mode of understanding for these experiences and their meanings. The aim of phenomenology is to directly describe unprejudiced experiences, rather than analyze, explain or generalizing them further. Qualitative interview can give access to these kinds of experiences.

### 8.3.4 Hermeneutics

Hermeneutics is the study of interpretation and understanding of texts, actions and conversations (Kvale 1996). Hermeneutical interpretation aims towards common and valid interpretation of the intended meaning of studied content. In this way, common understanding can be reached. In research interviews hermeneutical interpretation can be utilized at two different stages; interpreting the conversation as the interview is being conducted and interpreting the transcribed text of the interview.

The hermeneutical circle of interpretation describes the “dialog” between the researcher and the research data. The aim of this dialog is to create knowledge. Meanings can be determined in this infinite process (circular), which ends when the most sensible meaning has been reached. Meanings can be formed separately of different parts of the data and in totality. There exists continuum between phenomenological description and hermeneutical interpretation. With these methods interpretation of certain experiences in qualitative research can be done.

### 8.3.5 Framework analysis

Framework analysis is partly deductive and inductive. The objective of the study is the starting point in framework analysis (Pope et al. 2000). Thus the coding phase and identification of key issues is usually deductive in nature and aims to create summaries

of the raw text. The text is managed by indexing it and creating themes inside a thematic framework. These can be rearranged to form charts for each theme. Finally, mapping and interpretation of the charts is done. This phase can be deductive and/or inductive as associations between themes can be done based on the objectives of the study or they can emerge from the charts.

### 8.3.6 Grounded theory

Grounded theory is a method, developed by Barney Glaser and Anslem Strauss in the 1960`s, to form a theory from qualitative set of data by identifying the underlying structure of experiences (Elliott and Lazenbatt 2005). Grounded theory consists of different methods: concurrent data collection, constant comparative analysis, theoretical sampling and memoing. Some of these methods are widely used in other qualitative analysis, but only when all these methods are applied together, the approach can be called grounded theory.

Special characteristic for grounded theory is that data collection, sampling and analysis are a continuous cycle. As data is collected, it is analysed immediately and the next sample can be determined based on the analysis of the prior sample. In this method an inductive approach is used to code and analyse the raw data through memoing. This way after several “rounds” of data collection, sampling and analysing a theory is formed, which is grounded in the area of studied phenomena.

# 9 SUBJECTS AND METHODS

The starting point for this research was to examine the utilisation of internal audits and how internal audits could be used to monitor and guide the QMS. Qualitative approach was found to be most suitable for this kind of research topic. The choice of interview and content analysis as qualitative research methods was based on the research question and the aim of the study.

## 9.1 Study design

Qualitative interviews were conducted in spring 2011 at Orion (Espoo) to get information on the research questions. Semi-standardized open-ended interview approach was chosen as the method for collecting data and qualitative content analysis was chosen as the method for analysing qualitative data. The overall study design is plotted in the Figure 29 and the different parts of the study design are described in detail in this chapter.

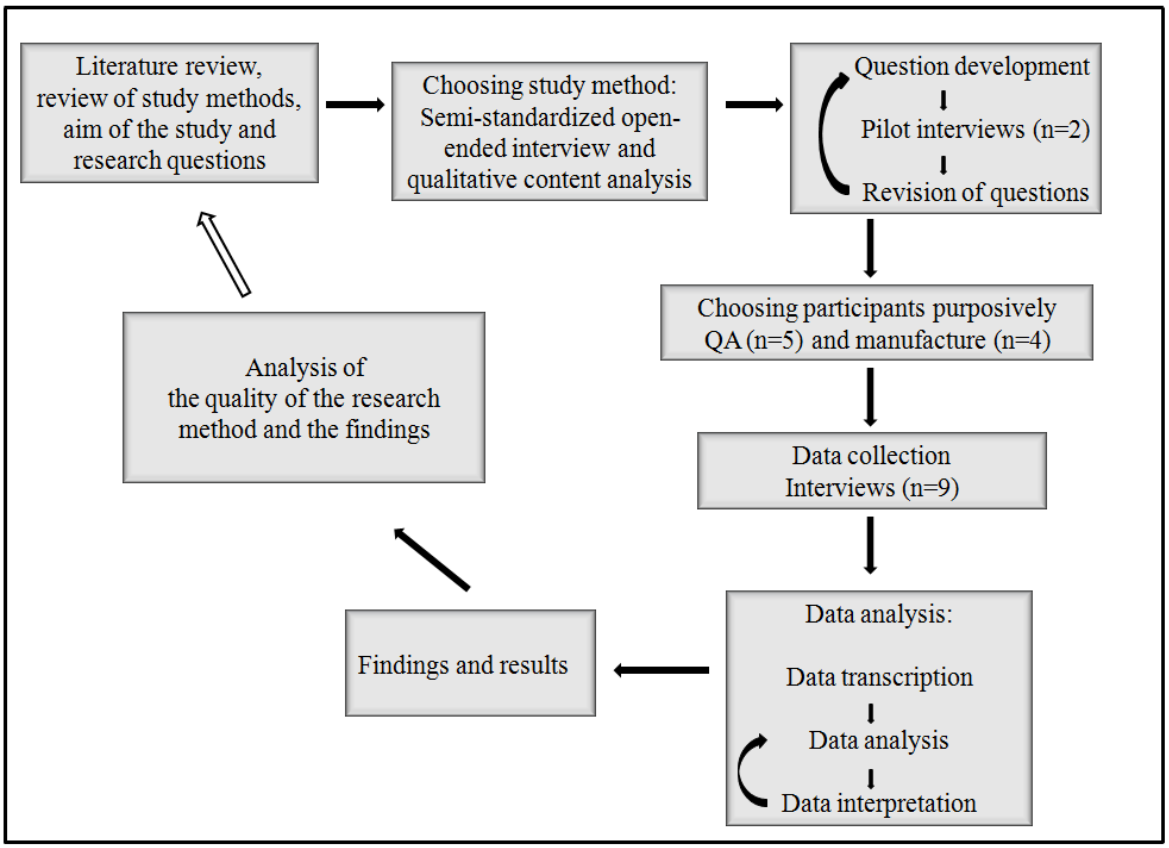


Figure 29. Flow chart of the overall study design.

## 9.2 Subject, population and sample

This work, including the fieldwork, was done at Orion`s headquarters in Espoo, Finland. Orion is a medium-sized pharmaceutical company which develops, manufactures and markets proprietary and generic products for the Finnish and global markets. All the interviewees (n=9) in this study are employees at Orion and work with quality related issues at the site in Espoo. Purposive sampling method was used to choose the interviewees. This was considered to be most appropriate since expert knowledge and experience on audits was necessary to gain qualitative information from the interviews and to provide a range of perspectives. Interviewees were selected from both auditor and auditee side and they had their background in QA or production. The appropriateness of sample size was evaluated with data saturation and this is further discussed in the Discussion chapter as part of the reliability assessment of this work.

## 9.3 Questionnaire development

Detailed review of study methods gave support to question development. Literature review and the aim of the study also assisted with this process. The research questions needed to be carefully planned as this was the most crucial part of the whole interview design (McNamara 2009, Turner 2010). Focus was given to the wording of the questions to develop open-ended, neutral and clear questions.

The format of the interview was chosen to be semi-standardized open-ended interview. The interview schedule included certain basic questions, which were asked from every interviewee in this study. The order of these questions was also planned in forehand. This schedule was developed by a team of people, including the interviewer/researcher and two experts from the pharmaceutical case company (one from QA and one from Generic Development & Product Lifecycle Management). Baseline for this question development was found in the literature. The build-up of an individual audit (Figure 21) and how audit is part of QMS and is commensurate with its elements (Figure 13) formed the main frame for question development. Also SOPs and practices related to

internal audits were considered as the questions were processed. The aim of the study was kept in mind through this entire process.

Additional and specifying questions were also asked based on the interviewee's answers. These questions were not outlined in the interview schedule as these questions depended on the answers and were asked on-the-spot. This is why the approach is called semi-structured and not structured, because the interviewer had to adapt to the interviewees answers. Although the order of the questions was determined in forehand, it could differ a bit from the schedule if the topic came up earlier in the interview. With a more flexible interview schedule, the interview became more "natural" and less formal.

### 9.3.1 Pilot interviews

The interview schedule was tested before conducting the research interviews. Pilot test revealed the functionality of the interview and gave a chance for the interviewer to practice interview skills (Kvale 1996). Interview was piloted with two interviewees. These participants were chosen because they both were experienced in audits. They also had similar background as the participants of the study (one from QA and one from production). Pilot`s function was to make sure that the questions were understood and operating as planned. Based on the pilot test, revision of the interview schedule was made (changing the order and wording of questions) and the estimate for the duration of the interview was determined. As some modification was made to the interview schedule and interviewer was not previously familiar with the interviewing method, pilot interviews were not included in the study.

### 9.3.2 Analysis of the interview schedule

Analysis of interview schedule shows what the purpose of the questions was and what kind of information was gained with these questions. The interview schedule with the developed questions is attached to this work in Appendix 1. The interview schedule is divided into six different sections (section A - F).

The first two questions (in section A) were about the background of the interviewee. It was considered to be a good way to start the interview with open questions which were easy to answer to. This got the conversation started between the interviewer and interviewee. In the next section (B), more specified questions about the interviewee`s viewpoint to internal audits were asked. This helped to interpret also the later answers to questions about the audit and set them to context by knowing the interviewee`s perspective. With the help of these questions a better understanding of the whole audit procedure could be formed as different standpoints are compiled. These statements could be compared and they could complement each other. This gave information about the status of the internal audits practised at Orion.

The status of internal audits and its development was discussed further in section C. The goals and features of internal audits were considered and both good and challenging parts of internal audits were reflected on. These questions helped in understanding interviewees` view on the purpose, strengths and weaknesses of the internal audit process. In section D different stages of internal audits, ranging from the audit plan to audit report and follow-up, were looked at in more detail. The impact and meaning, which these stages have on a properly functioning and effective internal audit and QMS were considered from interviewer`s point of view.

In section E, the utilization of internal audits in accordance with the development of QMS was discussed. Benefits and utilisation of internal audits were brought forth and the proposition question was asked ("Can internal audits affect the monitoring or guiding of QMS"?) At the end of the interview the interviewee was given a change to add to what was already said or to bring a new viewpoint to the interview which had not yet been covered (section F).

## 9.4 Data collection

Semi-standardised interviews (n=9) were done one-on-one at the interviewee`s work place at Orion in Espoo. All the interviews were held by the researcher. Interviews were recorded to ensure correct data interpretation. The duration of the interview was piloted

to be approximately one hour. The real duration of the interviews ranged from 25 min to 1 h 8 min.

Interviews were ethically conducted. The interviewees were informed about the motif for the research and the participation to this study was voluntary. The aim of the study and reason for the interview was briefly explained both via e-mail when the interviews were scheduled and in the beginning of the interview. At these points interviewees were also notified about the recording of the interview and they were asked as the interview took place whether the interview could be recorded.

An interview schedule, made during question development, was followed during each interview (see Appendix 1). In addition to the schedule, a brief introduction to the interview was given before each interview and in the end of the interview the interviewee was given a chance to ask any questions related to the interview or the study method from the interviewer. Permission to send e-mail to ask specifying questions about the collected data was asked at the end of the interview.

## 9.5 Data analysis

The data analysis process was a combination of different approaches (Figure 30). At the core of the analysis was the qualitative inductive content analysis. Memos were written alongside the analysis phase and this supported the analysis (based on grounded theory approach). The findings were gathered in an index frame (similar which is used in framework analysis). In addition to content analysis, quantitative analysis, deviant case analysis and testing of the proposition were conducted. Data analysis was guided inductively by closely reading the transcripts and letting findings emerge from the raw data, and also partly deductively by taking into consideration the objectives of this study, the interview schedule and testing the proposition.

Analysis and interpretation of data was on-going with the data collection which also helped to determine the saturation point of the data. Interpretation of the results emerging from the data analysis was done partly along side with the interviews and

analysis. Comprehensive data treatment, quantitative analysis and deviant case analysis were done to help improve the analysis of the data (Silverman 2007). As coded text was placed in categories, it was constantly compared with the content of that particular category. This supported the formation of categories which were clearly defined and distinct from one another.

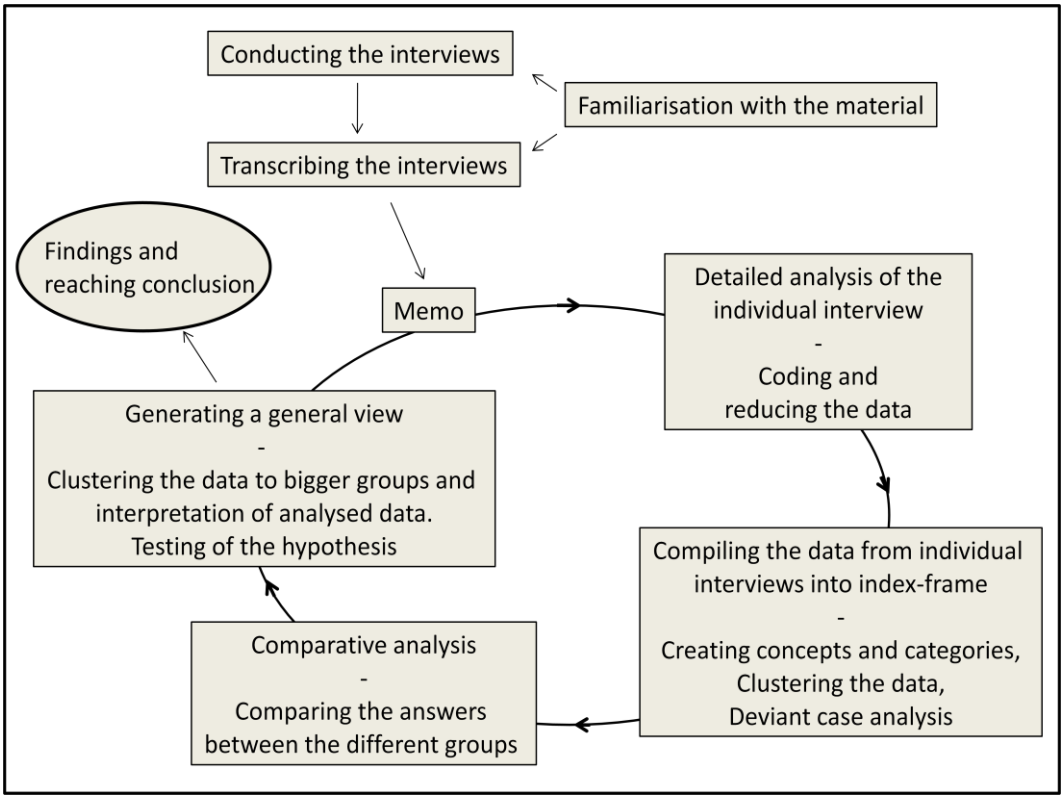


Figure 30. Data analysis process.

### 9.5.1 Transcription and memos

The recorded data from the interviews was transcribed verbatim by the interviewer. The familiarisation with the material started already in the interviewing phase and continued through the transcription process. The transcribed text was fixed to have the same layout (same font, margins, separation of the interviewer`s and interviewee`s texts).

After the interview and alongside with process of transcription, coding and categorising, memos of the interviews were written. These memos included comments and remarks about the interview situation, connections to literature review and raised other ideas

regarding the research questions. These memos were used later in the final phase of the data interpretation when data (views, and explanation and proposition) was grouped together.

### 9.5.2 Qualitative content analysis

The individual interviews were read through several times in order to understand and interpret its contents properly. These separate interviews were firstly analyzed by considering, whether the interviewee answered to the specific questions or did the answers pertain to something else. Secondly, the answers were analysed by considering how its importance was emphasised. Segments of texts (words, sections and whole sentences as quotations) were then coded and compressed. The coded data contained only the substantial information, but without losing too much relevant information.

The coding frame was formed inductively alongside the coding process to support uniform coding of the interviews. This coding frame and the general outline of the coding process are shown in Appendix 2. As the coding frame was complete, another round was made to code all the interviews according to the final frame. Alongside these coding rounds the saturation of data was evaluated. Data was considered to reach the level of saturation as new ideas were no longer brought forth and some of the already mentioned ideas were repeated several times. Coding process was tested by another coder from the research team with one transcribed interview. This was done to confirm the reliability of the coding process. Agreement was found in 65% of the total amount of codes. In these cases the codes were exactly the same. The rest of the coding (35%) had some dissimilarity. Most common reason for different coding was that a different text segment was coded, thought it handled the same subject. Mixing of categories for development of internal audit (18), management of internal audit (22) and development of operations explained some of the reasons for different coding. Also the categories for flow of information (16), training (24) and distribution of knowledge (11c) were tangled. A stricter separation of coding categories could have prevented some of these dissimilarities in the interpretation of the raw data.

Analytical categories were identified as the coded text segments were compiled and grouped into an index frame processed with Excel (Hämeen-Anttila and Katajavuori 2008). This was done with “copy & paste” method by using Excel. The index frame is shown in Appendix 3. Index frame contained section for the name or description of top and sub categories. It also included a place for coded text segments separately for both QA and manufacturing. Own sections for notes, deviant cases and numerical information were also created.

As more information was grouped into a category (top or sub), it was given a name or a short description. The contents of the information gathered in a category were constantly compared with what already was in that particular category. This way, similar information about a matter was grouped together. Also contradictory information was considered. All the sub categories were formed inductively as different themes emerged from the material. The top categories were formed partially inductively and deductively after the structured interview schedule. Finally, sub categories containing different views within the same theme were reorganised and merged to create top categories in the index frame. Top categories were distinguished from one another by constantly comparing what went into the categories and by describing the categories. The linkages between these different top categories were evaluated after the categories were formed.

### 9.5.3 Quantitative content analysis

Quantitative data analysis was considered to be good addition to qualitative content analysis. Cases and mentions were calculated to assess the importance and conformity of the results. Multiple similar opinions made by a single person were calculated as one. This way, information was gathered about how coherent or variant peoples` opinions were. Not just how many times these opinions were mentioned and emphasized.

Chi-square test can be used for frequency data and it shows the likelihood of the distribution of values into categories by chance occurrence (Gliner et al. 2002, Lewis

and Burke 1949). The formula used to calculate chi-square is $\chi^2 = \sum \frac{(O-E)^2}{E}$, in which O stands for Observed frequency and E stands for Expected frequency.

Insufficient categorization of the measures, more than two categories being compared and small expected cell frequencies limit the accurate use of chi-square test (Delucchi 1983, Kimmel 1956, Lewis and Burke 1949). As a requirement for chi-square test the measures need to fall independently into different categories and expected frequencies need to be of reasonable size. It is recommended that the number of expected frequencies should be over five when using chi square test, but the test has also been "found robust with small expected cell frequencies" (Camilli and Hopkins 1978).

In this study data was analysed by chi-square in order to detect independence or dependence of the background of the interviewees (QA and production) to the distribution of the opinions. It pointed out whether the answers were considerably different among these two groups because of the influence of their background. The null hypothesis was that the answers are independent of the background of the interviewee and suggest that there does not exist a relationship between these categories. This hypothesis is then either accepted or rejected depending on the result of the test.

Chi-square tests were done with Excel by categorizing the data into 2 X 2 or 2 X 3 contingency tables and doing the CHITEST. Observed values and expected values (statistical values calculated based on the observed values) were compiled in contingency tables to allow calculations. Then the value of the test was compared with chosen level of significance, in this case the p-value of 0.05. P-value indicates the probability that a result could be affected by chance. The null hypothesis is rejected if the CHITEST-value is lower than the chosen significance level ($p<0.05$). More information about this method and all the chi-square tests are shown in appendix 4.

### 9.5.4 Deviant case analysis

A place was created for deviant answers in the index frame so that counter opinions could be easily seen from the index frame. The reason behind a deviant case was investigated and taken into consideration as overview of the research data was formed.

### 9.5.5 Testing of the proposition

Classic quantitative hypothesis testing is based on statistical testing of results and aims to confirm or discard the hypothesis and generalize this finding. Proposition in this study can be considered more as a presumption than a classic hypothesis. This is due to the qualitative nature of this study. Two propositions were set and these are shown in Table 9.

Table 9. Proposition for this research

| | |
|---|---|
| 1 | Internal audits can to control/monitor quality systems. |
| 2 | Internal audits can guide quality systems. |

In this study, information concerning the proposition was drawn deductively from raw data (the transcribed interviews). This information either supported or was against this particular proposition (presumption). This deductively gathered information was categorised and all these categories were formed inductively and grouped together to form top categories (in the same way as with the content analysis). The terms under which the proposition is valid were considered in these categories. Also the concerns applying for an invalid proposition were taken into consideration. This way, positive and negative factors concerning the matter were considered, different nuances between monitoring and guidance were taken into account and diverse levels of monitoring and guiding were observed.

# 10 RESULTS AND DISCUSSION

In this chapter, description of the internal audit process is given based on the interviews. Also factors behind a functioning internal audit and the ways to utilise internal audits are evaluated and the proposition is tested.

## 10.1 Goal and description of the internal audit process at Orion

### 10.1.1 Goal of internal audit

The goal of internal audit and its fulfilment was discussed in the interviews. The goal of the internal audit can differ according to the main objective of the internal audit. Four main goals for internal audits appeared (Figure 31). Internal audits should be used to correct defects and reach compliance and internal audit should be as effective as possible. These viewpoints to defining the goal of the audit mainly came from the QA`s side. Development of operations was mostly suggested by the manufacturing personnel.

In some (2) of the interviewees opinion, the goal of internal audits was fulfilled with current internal audits. Most (7) of the interviewees thought that the goals were only partly fulfilled. The biggest obstacle in realizing these goals was mentioned to be the handling of corrective actions. Many of the interviewees stated that internal audits are capable to find what needs to be fixed, but taking corrective action to fix these deficiencies is difficult and challenging. Also the flow of information and audits not drilling deep enough were mentioned to be the cause for not reaching the goal of the internal audit. Two interviewees mentioned that as long as enough resources are available, goals set for internal audits can be met.

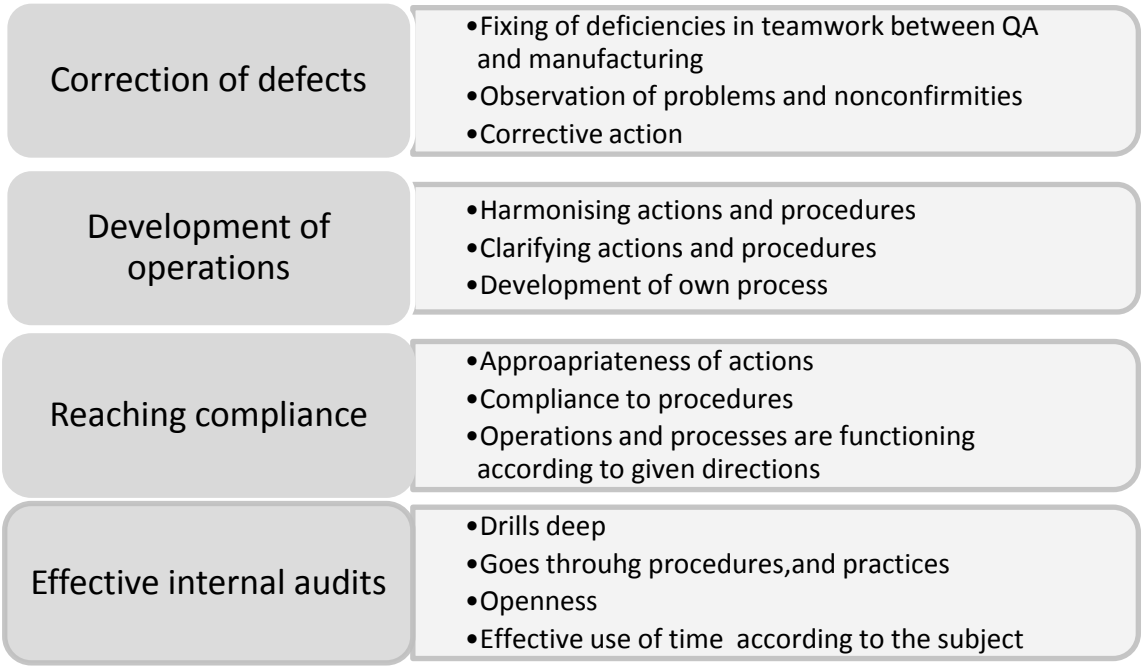


Figure 31. Goals of internal audits.

Goal of the audit could take the changing demands of the environment and management`s strategic goals into consideration. This way the goal setting itself might direct the internal audit to monitor and guide the QMS. As discussed in literature (Beckmerhagen et al. 2004, Kousek 2008, Morris 2008), audits are effective when the set goals are fulfilled. This in turn needs to be monitored and adjusted to gain a desirable outcome.

### 10.1.2 Different phases of internal audit process

Different phases of internal audit process were recognized. These consist of planning, preparation, on-site activities, report including audit findings, response and action to audit findings and follow-up and are presented in Figure 32. Managing the internal audit process and flow and distribution of information were emphasized and recognized as important supporting factors as the course of internal audit process was discussed with the interviewees.

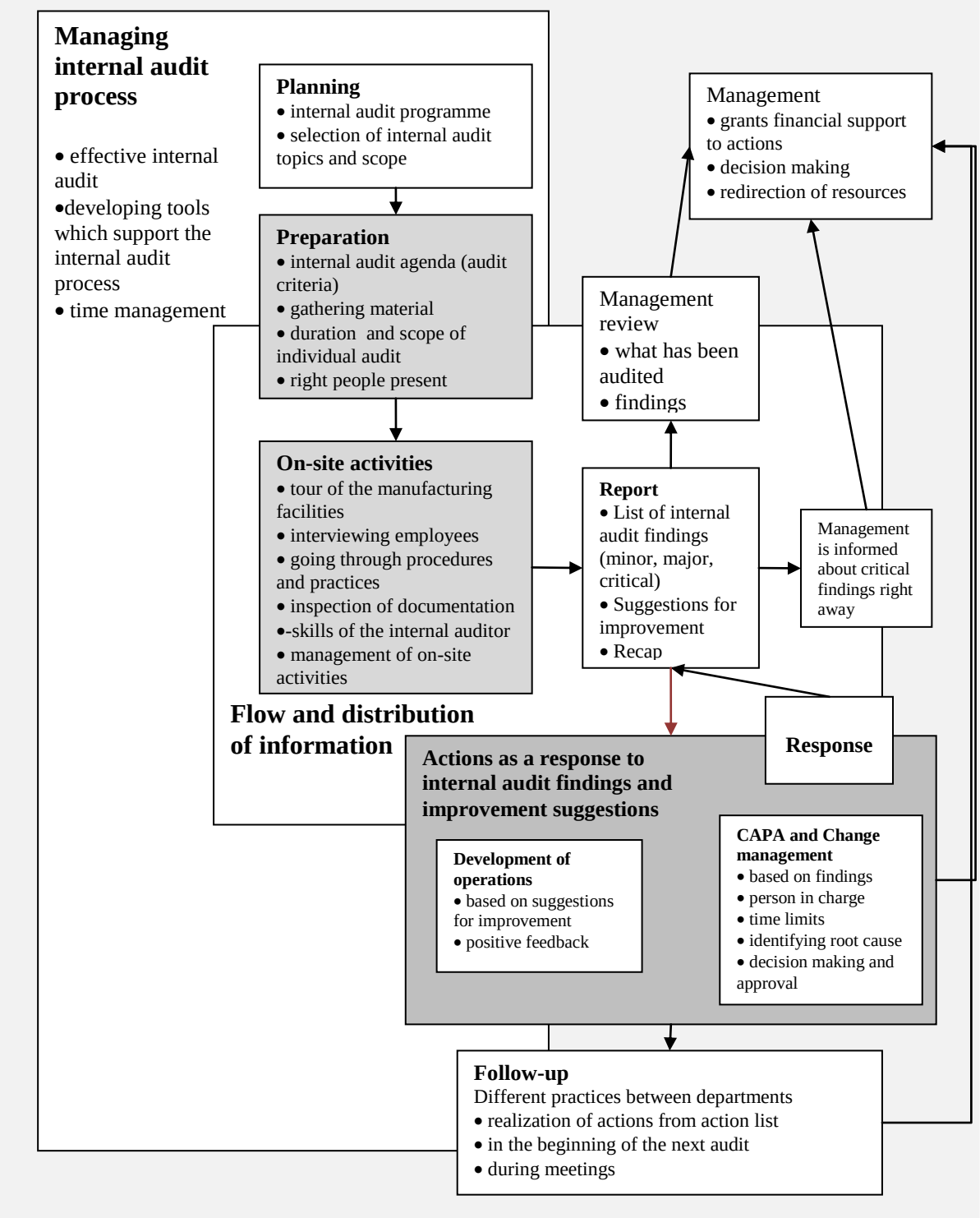


Figure 32. Internal audit process *

Internal audit programme is planned and developed annually. Topics are selected in cooperation with QA, manufacturing and engineering. The scope of an individual internal audit is set to consider a part of a process or a function and duration of on-site activities is couple of hours. This has also been found to be an ideal duration for an internal audit in literature (Askey and Dale 1994). Internal audits have a limited scope, because detailed information about systems is gathered in a reasonable amount of time (without disturbing the operations too much). Process or QMS audits, done internally by QA managers or externally by external auditors, have wider scope and take longer time as these gather information at a more superficial level.

Preparation to audit includes inviting the right people to be involved in the audit, making sure their roles and responsibilities are clear, communicating the audit agenda and gathering and familiarising with the material about the audited matter in forehand. Gathering of the materials is mostly done by the auditees and the familiarization with the material is done by the auditor. The employee whose work is being audited or who is being interviewed during an audit should be familiar with the important documentation regarding his/her work. It was stated that *"the one being audited should not be too prepared for the audit to be able to find out the true everyday practice".*

On-site activities depend on the type and scope of the audit and on the audit agenda (audit criteria). On-site activities usually consist of inspection of written material (documentation and procedures) and comparing this with observed practices (tour of the facilities and interviewing employees). Internal auditor is in charge of the schedule of internal audit activities. Internal auditor, in cooperation with internal audit team and production staff, detects findings and items for improvements.

The skills of internal auditors were considered important in the audit process and especially during the on-site activities (Figure 33). Interactive skills and managing the audit process with *"a sense of where the audit is going"* were mentioned as attributes required of a skilled auditor. The expertise of an internal auditor was most commonly emphasized. This makes sense in audits done in pharmaceutical field since a detailed

knowledge about manufacturing procedures and guidelines is essential to understand and monitor these functions.


Figure 33. Important skills of the auditor.

Report is made, giving a list of findings, improvement suggestions and a short summary. Based on this report management can be informed about critical findings and a review can be made about the contents of an audit report (management review). This report is distributed to audited side (production) as soon as possible so that actions to correct and develop the processes can be started without delays. Also a response is given where time limits and responsibilities are set for the actions. Investigation of the root cause of the finding and possible corrective actions are decided and implemented.

Finally, a follow-up is done to confirm that proper action has been taken. There exists different ways to do this follow-up. The simplest is to check the action list and to follow whether the actions are being realized or not within the set time limit. Also meetings (within the department or in cooperation with QA) can be held where the realization of actions is discussed. Final follow-up can be done in the beginning of the next audit. The downside of the last suggestion is that this takes time away from the next internal audit, the topic might be totally different and too much time has elapsed between making the finding and following up. At the moment, follow-up is not done to confirm whether and

how audit activities improved the audited system. This would demand more resources and some kind of indicator to be able to measure this change.

### 10.1.3 Managing internal audit process

The management of internal audit process is an important factor in the successful execution of an internal audit. In the interviews all the different phases: planning, preparation, on-site activities, report, action to internal audit findings and follow-up were mentioned when the management of internal audit process was discussed (Figure 34).


Figure 34. Effective audit can be reached by managing the different phases of internal audit process.

The management of each separate phase affects the overall management of the internal audit process. *"The better the internal audit activities are managed, the better the deficiencies can be handled and CAPA action defined".* It can be concluded from the

interviewees` answers that, for the internal audit to be effective, it has to be well organised, structured and scheduled. Together with clearly defined scope, topic, responsibilities and enough time for preparation this enables good time management of audit activities and more effective approach to discover and deal with internal audit findings. Similar opinions about selection of audit topics (Kausek 2008, Probitts 2000) and the importance of preparation (Askey and Dale 1994, Elliot 2007, Gupta 2006) for gaining the right information with the available resources was also mentioned in other research.

Effective audit can be reached by managing the different phases of internal audit process. Information about these phases should be utilised as feedback to develop internal audit process. It was expressed in the interviews that information about internal audits is also gained from external audits, as the internal audit programme and process is often evaluated by external auditors. According to other research this information could also be gathered in the form of survey after each internal audit from the people participating in the internal audit process (from both QA and management side) (Beckmerhagen et al. 2004, Rajendran and Devadasan 2005). Based on information gained from this work and literature, information gathered from external and internal audits could be used to develop the audit process to be more effective. This in turn could benefit the whole QMS, as effective internal audits would yield in more valuable information about the QMS.

Different phases of internal audit process (e.g. findings, root cause to findings, corrective action, and development of audit process) should be clearly distinct from one another (cf. risk management). It was expressed in the interviewees that only a certain group of experts should concentrate on correcting each specific area. When a certain group is focused on e.g. solving a problem, the workload is not scattered. This way time and resource management is more efficient. For this to work, it is important that each phase of internal audit is well defined and teamwork and the flow of information function well.

### 10.1.4 Flow and distribution of information

Flow and distribution of information throughout the course of internal audit process and especially about internal audit findings and corrective actions was considered to be essential part of the whole internal audit process. Outlined structure of the flow and distribution of internal audit information is presented in Figure 35.

People (QA, production, engineering) participating in the internal audit itself, gain first-hand knowledge about the audited system. Good communication amongst these people, especially concerning the audit process, allows a smooth flow of internal audit activities, scope and agenda. It has been expressed in the literature that people with first-hand knowledge should be invited to partake in internal audits (Morris 2008). It demands a lot of organisational skills to include all the right people to participate in the internal audit and communicating to them the importance of preparation e.g. to take enough time to prepare for the upcoming audit. It also depends on the participants, how much time they can dedicate to preparation. *"Taking hold of oneself and knowing how to prioritize own tasks"* was mentioned when it comes to preparation. Ultimately it is the individual`s responsibility to be prepared. If critical findings are made during audit, the management is notified immediately and the case is discussed in the organisation in question. It is the top management`s responsibility to ensure a functional QMS and the middle management caries out the activities of controlling the QMS.

Audit report including the action list is made to document the audit process. It is the main form of information distributed about the internal audit and its findings. This report is placed in document management system where it can be viewed by all interested parties. A summary report of audit findings is made including the accumulated internal audit findings and in some cases the corrective actions taken. This is mainly aimed towards management as it is part of management review.

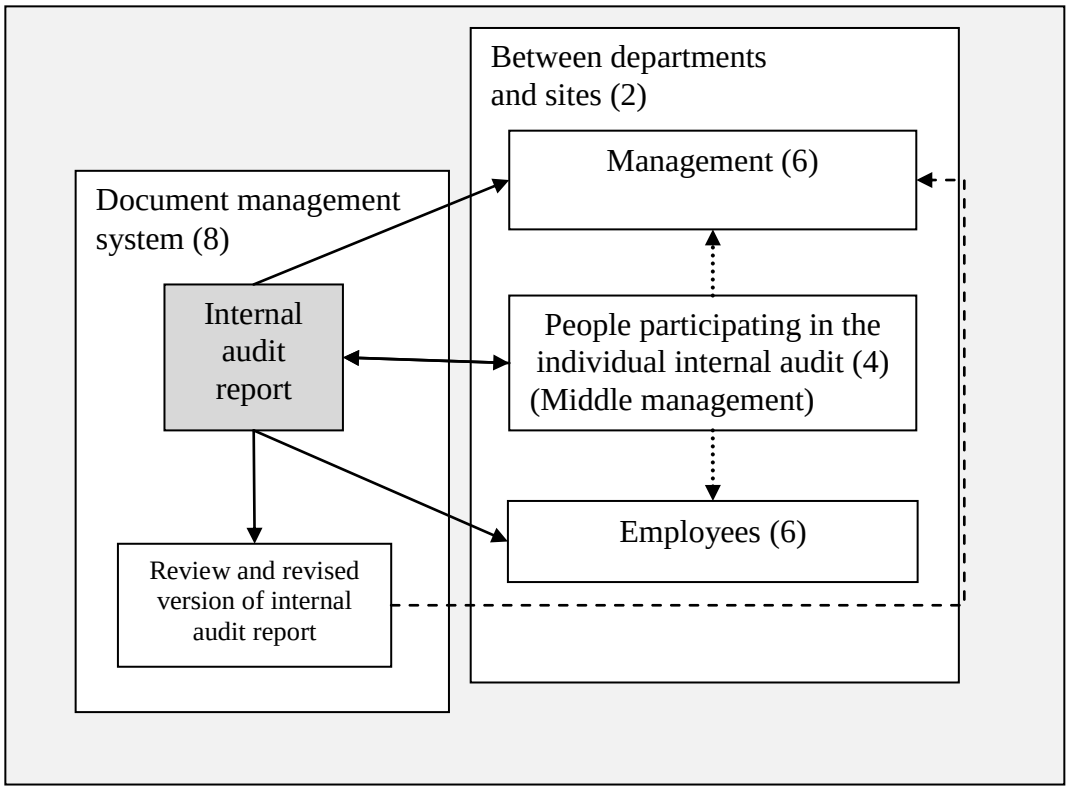


Figure 35. Flow and distribution of information*
*Number of opinions about information flow and distribution about internal audits is shown in parenthesis.
*Arrows show the distribution of information through data management system
*Dashed arrows show the distribution of revised and reviewed information
*Dotted arrows show the distribution of information from people participating in the audit

### 10.1.5 Well functioning and challenging aspects with internal audits

When asked what works especially well with internal audits and what are the more challenging parts of it, the following aspects of internal audit (shown in Table 10) emerged. Also reasons and possible improvement were considered for the challenges. Chi square test showed no significant difference in the answers caused by the background of the interviewees.

Teamwork and openness was expressed by almost all of the interviewees to be one of the strengths with current internal audit practice. Preparation phase of internal audit process was also considered to function well. It has also been expressed in the literature that strong links of communication and co-operation between auditor and auditee and support the overall audit process (Beckmerhagen et al. 2003).

Table 10. Functioning and challenging sides of internal audits.*

| Well functioning | Challenges |
|---|---|
| • Teamwork and openness (7/ca. 60%)<br>• Preparation (2/ca. 15%)<br>• On-site activities of inspection (3/ ca. 25%) | • Corrective actions (5/ca. 60%)<br>• Completion (2/ca. 20%)<br>• Management of on-site activities (2/ca. 20%) |

*The number of interviewees expressing this opinion/ the percentages of interviewers expressing this view is shown in parenthesis.

On-site activities received mixed reviews. Tour of the facilities and the overall conduction of onsite activities were considered to be successful and leading to a list of findings about the audited systems. The management of on-site activities concerning time management and drilling deep to gain detailed information was considered more challenging. Corrective actions and completion of the internal audit process was found demanding. It was expressed that corrective actions need to be done more effectively and that more focus (time and resources) should be given to complete these matters promptly. Especially the transition between the two phases, from the QA`s audit report with the action list to agreed findings to taking corrective actions, was recognized as being the most challenging part. In this transition the responsibility from QA shifts to production. Efforts to tackle this part have been mainly done in the form of follow-up. This way it is the internal auditor`s (QA) responsibility to monitor whether corrective action has been taken to internal audit findings and they make the decision about completion of internal audit.

Reasons for slow completion of corrections could be manifold and depend on the type of finding the specific corrective action relates to. Maybe the root cause is not found,

the new corrections are hard and time consuming to implement, or management should be more involved in ensuring the implementation. Especially top management`s commitment is considered as a crucial part of a effectively functioning QMS (Williamson et al. 1996). Other reasons for audit failures have also been discussed in literature e.g. poor skills of the auditor, inadequate preparation and timekeeping (Askey and Dale 1994, Karapetrovic and Willborn 2000, Ramly et al. 2008).

Corrective actions and analysis of problems have been identified as a weak area in the audit process and QMS also in the literature (Elliot et al. 2007, Gupta 2000, Markovitz 2010, Percy 2010). The role of management in making decisions and taking actions based on audit report is also important. Internal audits should be strongly integrated with CAPA and change management systems to allow the successful processing of all internal audit findings in a proper way. As discussed in the literature review, QA could have a more active role by consulting, counselling and training personnel (Skubch and Zimmer 2009). QA could take part in the problem solving phase and in finding ways to implement improvements, not just in the follow-up phase.

### 10.1.6 Important features of a functioning internal audit

The features discussed here were recognised as important in conducting a functioning internal audit (Figure 36). Openness and teamwork, preparation and on-site activities were already mentioned as positive and functioning parts of internal audit process. People involved in the audit process were seen as the most influential to the success of the internal audit. Especially the expertise and activity of people was seen as the driving force. Also the leading role of the auditor was recognised. Another important feature was the scope of the internal audit. The subject needs to be specified to be able to go through it in the set time frame and to gain detailed information. These results were predictable and similar features have also been found important in other work (Ramly et al. 2008).

The challenging sides of corrective action and completion of tasks were not mentioned here. Could it be that this activity is seen as a separate process from internal auditing or perhaps the question was understood to consider only important features regarding the discovery of internal audit findings?

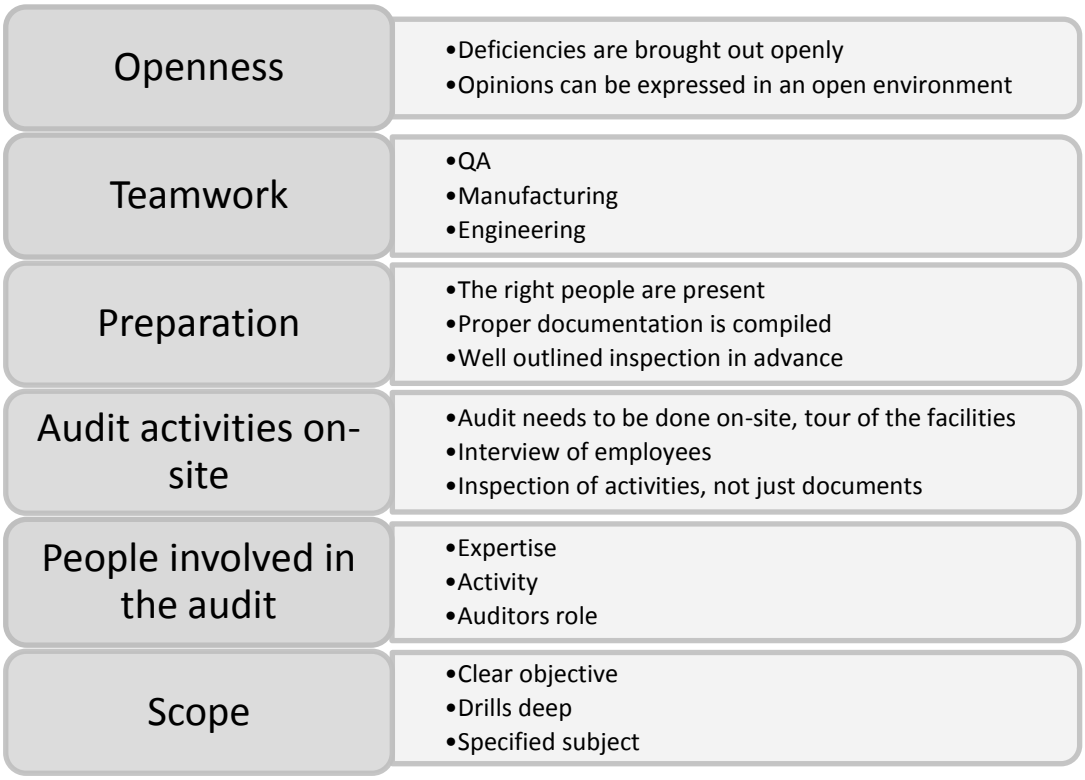


Figure 36. Important features of the internal audit

## 10.2 How internal audits can be utilised

One of the study questions was how internal audits could be more fully utilised to gain more information about own operation and QMS. Opinions about how internal audits are being utilised and ideas about how internal audits could be utilised emerged from analysed data. Seven main categories were recognized (Figure 37). Internal audits are/can be utilised to gain information, implement improvements, share information and practices, prepare for an external audit, develop the internal audit process itself, and large scale follow-up.


Figure 37. Current and possible utilisation of internal audits.

*Suggestions for the possible utilisation opportunities are highlighted in bold.

In addition to ideas about utilisation of internal audits it was proposed by the interviewees that a greater number of internal audits should be conducted to gain more information about QMS. This suggestion is reasonable, as larger amount of conducted internal audits represents a larger sample and could result in a more comprehensive picture of the status of QMS. But where to draw the line for a suitable amount of internal audits and which is more beneficial: to conduct more audits or to utilise the ones already held more effectively? Internal audit activities require a lot of resources, time and money and these should be used wisely. This is why better utilisation of current internal audits could be more beneficial than simply increasing the amount of internal audits.

### 10.2.1 Gaining information about own practices and improvement of operations

The two first categories show the most typical uses for internal audits. Internal audits are an excellent way to gain information and feedback about own systems, compliance and the reliability of operations. It was expressed in the interviews that feedback from internal audits helped to gain confidence as operations were made more reliable. Internal audit was also described as a learning process. Improvement of operations can be made based on the internal audit findings. Based on the type of finding a correction, improvement, rationalisation or development of operation or procedure could be made. This way these two categories are linked together. The more information gathered with internal audits, the better the improvements can be implemented.

### 10.2.2 Sharing of information

Flow and distribution of information was mentioned as being an important factor throughout the whole process of internal audit. Sharing of information related to the outcome of the internal audit should be utilised more effectively. Distribution of feedback information has also been emphasized in the literature (Saraph et al. 1989).

The main concern was that the information was considered not to have a wide-ranging distribution and that most of the valuable and detailed information stays only with the

group of people taking part in the internal audit activities. It was also expressed that mainly the same people participate in the internal audit process. It was suggested that more people should be involved and familiar with internal audits during the course of the year. It was also proposed that information should be distributed more actively to clearly defined parties (employees and management of the department), not just by placing it into the document management system. Information should be easily accessible and retrievable to aid in decision making (Fowler 1995, Liu and Xu 2001). It was also discussed that active distribution of information should be included in the SOP for internal audits. The different ways to share information gained in internal audits are shown in Figure 38. In addition to this it was also mentioned that feedback information from internal audit could be utilised to develop the internal audit itself.

A lot of information is gained from a single individual audit and some of this information is put on paper in the form of a report and from this report some of the information is compiled in to a review. Information presented in these documents needs to be clearly defined. Valuable information must not get lost, it needs to be recognised and highlighted. It was suggested in one of the interviews that a system should exist, where accumulated information throughout the year should be effortlessly gathered. *"When there is a demand for this information from different sources, the realisation of internal audits, both the amounts and findings, could be accumulated during the year"*. There is a demand for retrieving information easily and to use it to aid in decision making. This way information about several internal audits can be compiled and this could give a more comprehensive picture about the current status of QMS and even facilitate better follow-up such as following trends.

Information to management was also discussed in the interviews. In conclusion, this information can be divided into two categories. Firstly, information about the held internal audits topics in the form of management review and the findings are communicated to management. This can give an overall picture of the weaknesses and strengths discovered about own systems (monitoring the QMS). Secondly, information and suggestions about the execution of corrective action and improvements based on internal audit findings should also be communicated. This is due to management`s

needs to make decisions about redirecting or providing resources to fix or improve the audited system (guiding the QMS). This analysis reveals that information about controlling (monitoring and guiding) QMS can be communicated to management level.

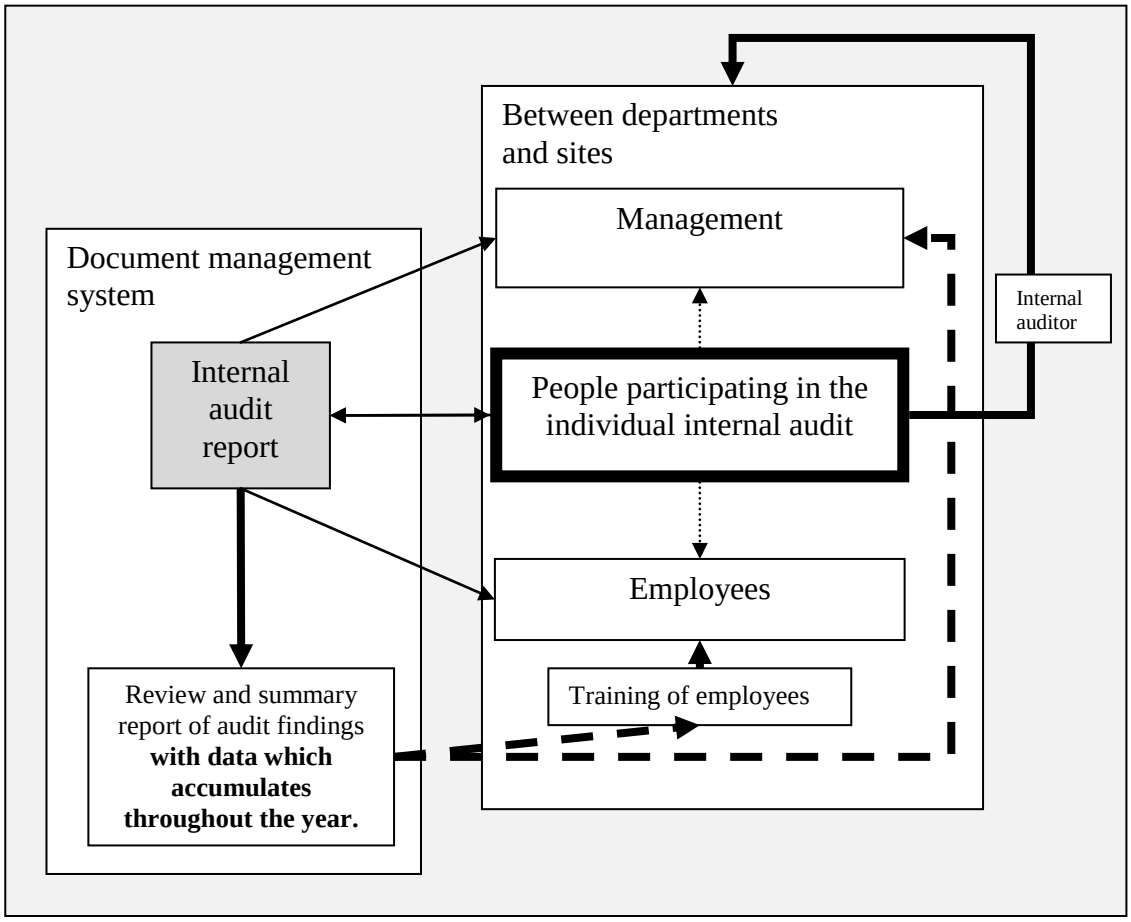


Figure 38. Ways to share the information gained in internal audits (Forming a report with accumulating data, sharing the information to management and employees, internal auditor`s role in distributing information to other departments and sites.).

Ideas about going over the internal audit topic, findings and corrective actions with the employees were expressed in the interviews. Training and team meetings were mentioned as ways to distribute the information forward to employees. This was seen as a way to prevent future deficiencies and make employees aware of why corrective action is taken or improvements are done. This could also make the process of corrective action smoother and make employees more aware of their own operational systems. It is important to remember that manufacturing employees work on different

shifts and this could make it challenging to train and distribute information effectively to all employees.

Also sharing of information related to internal audit findings, improvement suggestions and good practices between departments and sites was mentioned. If the information is distributed flexibly without boundaries between different departments and sites, this information can be accumulated and utilised to gain knowledge about own systems and develop these further. In this way internal audits can be considered as a learning process (Alic and Rusjan 2010). Internal audits are laborious to conduct so all the information about the whole organisation`s internal audits should be utilised more effectively.

The responsibility of this information distribution was also discussed. Internal auditor was seen as being at a good position to share and distribute information flexibly between departments and sites for example during internal audits. The training and communication towards employees was seen as a responsibility of the audited departments themselves.

### 10.2.3 Sharing of operational practices

With the help of internal audit a lot of information about operational practices is gained. Although the procedures might be the similar, the practices might vary from department to department and especially between sites. The reason for establishing different practices is that the functions of the departments might be different. QPs might not even be aware of different practices existing at the different sites or departments because they are usually assigned to audit only their own departments. Sharing knowledge about different operational practices can help integrate best practices throughout the organisation (Lubit 2001).

Ideas about harmonisation of operational practices, spreading best practices and sharing know-how emerged from the interviews (Figure 39). As mentioned earlier, internal auditor has an ideal opportunity to examine different practices. Internal auditor should be aware of the different practices within the company, not just the one department,

which internal auditor is responsible for. Cooperation between internal auditors from different departments and sites is needed as their knowledge can be utilized to harmonize operations and spread practices and know-how. It was suggested that internal auditors could widen their view and gain more experience by participating more in each other`s audits. This way internal auditor (within the same company, but from different department or site) can contribute with important viewpoints and know-how about practices to the audited field and gain experience to use this knowledge in their own department or site. It was also expressed that information is distributed better through internal auditors themselves than by reading and interpreting reports of audits and different practices.

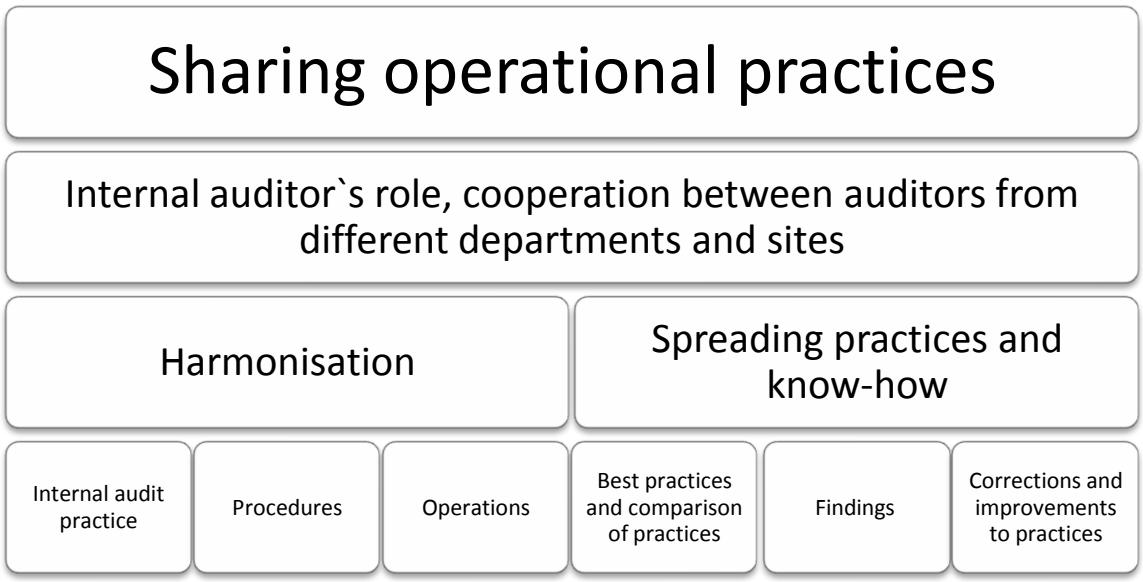


Figure 39. Sharing and spreading operational practices with the help of internal audits throughout the organisation.

Internal audit was seen as an opportunity to harmonise operations. Firstly, internal audit practices should be harmonised. By harmonising internal audit procedures and tools a similar and comparable data can be gained from the audits. Secondly, procedures which guide operations are harmonised and thirdly the operations themselves are harmonised.

Quality system audit, common internal audit topic and internal auditors participating in each other`s audits were seen as ways to achieve harmonisation of operations. It was

considered easier and more effective to control operations, if there are common procedures and practices. Harmonized operations could also be more easily developed further and compared with one another.

If a detailed procedure is used to cover every field, it does not necessarily harmonise operations in a preferred way. What works best in one department might not work at another. This is why some variation in procedures and practices (between departments) is good and the procedures should not be too strict. If a procedure exists, it is important to comply with it. In pharmaceutical industry it is too risky to have varied operational practices (within a department) as this can lead to inconsistent quality. Variation can also make it harder to control these operations. Sometimes (with good reason) it might be wise to change the procedure to better describe the actual operations, to be able to control and harmonise operations.

Internal audits were also recognised as being able to spread practices and know-how by recognising best practices, distributing information about internal audit findings and sharing ideas about possible corrections to these findings.

Conducting the audit according to the concept of appreciative audit and distributing this information may lead to “internal benchmarking”. Gathering information about best practices together with sharing of knowledge and know-how between departments allows the sharing of operational practices. Also comparison of practices between departments and sites can be done. One way to harmonise operations might be through observing different operations and choosing the best practice and spread this practice through the organisation by taking it into account in the procedures.

All the departments function within the same QMS and if findings concerned with QMS are made in one department, these problems might occur also elsewhere, at a different department or site. Therefore it was suggested that if a finding is made in one department, the others should be informed so they could find out, whether they had the same issues. This way corrective and preventive action of operational practices throughout the organization can be taken based on one single internal audit finding.

These could be executed in the form of self-audit or as an internal audit in the next years internal audit programme. If the finding is critical in nature, the actions should be rapid to check, if the problem exists throughout the system. Thinking about this from another point of view, it could also be thought, why the problem does not exist in some departments with similar operations and try to learn from them.

Also knowledge and know-how about taking CAPA and handling improvements should be shared. If a problem occurs, the solution might be found from the different ways to manage the issue. Why not utilize the information and know-how already present within the organization and try to utilize the existing good practices. As said by one of the interviewees *"It should be gone through whether other departments or sites have had similar problems and if these have been smartly corrected. If the wheel has already been invented somewhere else, it would be nice to spread this information around. This does not cost any extra, on the contrary".*

### 10.2.4 Preparation for an external audit

Internal audits were discussed concerning other audits done by external auditors. Here the term external audit includes both external audits done by partners and external inspections done by authorities. External audits were considered by the interviewees to be stricter and more effective compared to internal audits. Wider scope of external audits and having more rapid reaction to external audit findings in the form of improvements and corrections were seen as ways to control the QMS better than with internal audits. While internal audits were considered better in discovering findings because issues could be discussed more openly. Though, internal audit was seen sometimes as incapable to fix these issues before the same findings were made again in external audits.

Internal audits are not formally used as a preparation to external audits at Orion. The reason for this was that internal and external audit programmes are based on different annual programmes and these two types of audits exist side-by-side as separate

processes. If a new type of external audit finding is made, it can be picked up as an internal audit topic for the next annual internal audit programme.
Internal and external audits focus partly on the same areas and these both aim to monitor the audited system. This common ground makes it ideal to utilise external audits with regard to internal audits, and vice versa. Also a more comprehensive picture about QMS could be gained by gathering information from external and internal audits.

The functionality of internal audit process can also be evaluated by comparing the findings made in internal and external audits. If a finding is made in external audit, but not in internal audit, internal audit might be considered insufficient. If the same finding is made in both audits, the correction and improvements in internal audit process might be considered inadequate. Even the whole internal audit process could be the topic of an external audit. This way valuable information about the whole audit process is gained as it is investigated.

Internal audits should be able to detect and resolve deficiencies, before these are noticed by external auditors. Going through the operations at a rough level and examine previous findings from internal and external audits is done as a preparation for an external audit. This preparation can be done unofficially and independently by the department or in cooperation with QA. An official internal audit as a preparation to external audit is harder to conduct as this has to be done well in advance in order to manage to resolve all the findings uncovered in the internal audit. Also the internal audit programme is not flexible enough to allow “extra” audits to be done in short notice so these pre-audits cannot be planned into the programme. This again might delay the internal audit programme schedule, if it is set too tight. It is important to plan and develop the entire internal audit process to be adjustable to changes.

By conducting internal audits effectively and utilising the information from internal audits already done, the need for extensive preparations might diminish. Selecting the audit topics by taking into account the changing environment (regulations, new technology), continually developing the audit process to be more effective and having enough resources to react to internal audit findings ensures a fully functional internal

audit. This way findings can be picked up and dealt with before the external audit takes place. This was appreciated (in the interviews) as giving confidence to go through the audited field with external auditors, if it had been looked over successfully in an internal audit.

### 10.2.5 Development of internal audit practices

During the course of the audit process, audit experience and knowledge of auditing is gained. This knowledge can be utilised to develop and improve the internal audit process. The development and managing of internal audit process has been previously mentioned in accordance with the description of audit process, harmonisation of operations and utilisation of external audits. It was emphasized in the interviews that auditor`s skills are improved by gaining experience from doing audits, the audit process enhances cooperation between different departments and groups of people (QA, manufacturing, engineering). Internal audits were also seen as a way to select future internal audit topics by discovering strengths and weaknesses in procedures and operations.

### 10.2.6 Follow-up

Internal audit findings lead to extensive decision making, action to correct or improve these findings and finally a follow-up is done to ensure that action to findings have been completed. In this sense, follow-up has an important role in ensuring the completion of the whole audit process. It is the responsibility of internal auditor to do this follow-up although the actions to correct or improve the finding lay with the managers of the audited side, which is responsible for the operation in the first place. Usually the interest is whether action has been taken or not. It is not formally questioned or reported what kind of action has been taken, has the root cause for the finding been found and how to monitor the actions further to see, if the audited system was improved or fixed. These issues are discussed in separate meetings between departments (QA and production) in so called CAPA-meetings. Also external findings are discussed here. This way a comprehensive picture of the department`s functions can be achieved.

Information from internal audit follow-up is utilised in reports and reviews. The current reviews include the completed audits done over the year and in some cases also the internal audit findings. Arisen internal audit findings together with external audit findings could be gathered from different departments and sites to try to monitor trends. Also information regarding the follow-up of the effects of audit actions could be done. This has also been suggested in literature (Percy 2010). This way it could be found out what benefits the audit had on the audited system. Information about what kind of action has significant effect on the operations should be taken. This way improvements and action which are noteworthy can be executed and resources would be focused on these rather than to actions which in the interviews were referred to as *"temporary plaster-solution*".

In order to do follow-up of audit activities, the effect of internal audits should be measured. Also to be able to do follow trends and compare the results of internal audits between departments and sites some common indicators should exist. It was expressed that indicators could reveal either the status of the internal audit process or about the audited subject. This was one of the reasons why the measuring of the effect of internal audit activities and gathering comparable information about internal audit findings was found so difficult.

It was suggested that possible indicators could be the amount of findings are made, amount of notifications and external audit findings. The amount of findings needs to be adjusted with the criticality of the findings, the total amount of findings made in that particular audit and total amount of audits made in that field. This way comparable information might be gathered. If many findings are made during audit, it cannot be assumed that the audited system is in bad shape or to compare this audit result with previous audits or other departments. High number of findings might be due to a lot of reasons. The audit process itself might be functioning so well that it is able to discover findings. The auditors have different approaches and this affects the amount of internal audit findings. The severity of audit findings might be considered differently from audit to audit and the duration and scope of audit may vary. It was also expressed that unified

system for follow-up and harmonized operations allows for more effective follow-up and gathering of comparable information.

### 10.3 Do internal audits monitor and/or guide quality systems?

Both propositions were tested by gathering positive and negative factors contributing to monitoring and guiding quality systems with internal audits. The conditions under which these propositions are both valid and invalid were examined further. As part of proposition testing a chi-square test was done to determine the influence of the background to the interviewees` answers.

#### 10.3.1 Internal audits monitor quality system.

All the interviewees (9) concurred with the proposition, which stated that internal audits monitor quality systems. The following four conditions emerged: selection of internal audit topics, monitoring on the grounds of internal audit findings, utilisation of internal audits and flow and distribution of information. These are presented in Table 11.

Table 11. Positive and negative factors contributing to monitor quality system with internal audits*.

| **Factors contributing to monitor quality system with internal audits.** | **Positively** | **Negatively** |
|---|---|---|
| 1. Selection of internal audit topics (8) | Diversified selection of topics, comprehensive set of audits (6) | Narrow selection of topics, isolated individual audits (2) |
| 2. Monitoring on the grounds of internal audit findings (7) | Multiple internal audit findings can give signals about the state of QMS, identify places for improvement, bring forth information about own systems and activities not gained elsewhere, finding out whether or not procedures and instructions are being followed. (4) | Too small-scale and detailed information to be linked to the QMS. (3) |
| 3. Utilisation of internal audits (2) | Enough time to form a recap and reflect on the audit findings from multiple individual audits. (2) | - |
| 4. Flow and distribution of information (2) | Information to top management regarding the internal audit findings.<br>Auditor`s role as information distributor during the audit. (2) | - |

*Number of interviewees considering the condition relevant are shown in parentheses behind the text (One comment per matter (either negative or positive) was counted as one). Factors are presented in the order of importance.
- No comments were made

### 10.3.2 Internal audits have the potential to guide quality systems.

Many of the same arguments were given to the proposition with the regard to guiding quality systems with the help of internal audits as for the first proposition where the monitoring was considered. These are presented in Table 12. Some interviewees answered to these propositions with one common answer and some answered separately for each proposition. Also slightly different factors were found for the aspects of guiding the quality system with internal audits. The main differences existed in the way opinions were expressed e.g. *"there is potential"* or *"it is the intention"* to guide QMS with internal audits. The interviewees were more uncertain with their view on internal audit guiding the QMS compared to monitoring it.

Table 12. Positive and negative factors contributing to guiding quality system with internal audits*.

| **Factors contributing to monitor quality system with internal audits.** | **Positively** | **Negatively** |
|---|---|---|
| 1. Selection of internal audit topics (8) | Diversified selection of topics, more systematic planning of comprehensive set of audits (6) | Narrow selection of topics, isolated individual audits (2) |
| 2. Guiding on the grounds of internal audit findings (7) | By correcting procedures based on internal audit findings, operations and practices can be corrected. Identifying and implementing improvement. Action can be taken preventively as totally new information can be gathered with internal audits. (3) | It is more challenging to guide systems than action, external audit findings might have bigger impact than internal audit findings on QMS, internal audit findings can be hard to link with QMS (4) |
| 3. Flow and distribution of information (4) | Information to top management regarding the internal audit findings to redirect resources to the weaker areas. Communication about corrective actions towards top and bottom. Auditor`s role as information distributor during the audit. (4) | - |
| 4. Utilisation of internal audits (4) | Internal audits have the opportunity to guide QMS, if utilised better. Internal audits may also guide the culture of company and workings and even enforce or maintain QMS by keeping it up-dated with the changing environment. (2) Enough time to form a recap and reflect on the audit findings from multiple individual audits (2). | - |
| 5. Management and organisation of internal audit activities (2) | Effective internal audit, time and resources for the execution of internal audit activities and the implementation of corrective actions based on internal audit findings. (Also considers selection of internal audit topics and flow of information) (2) | - |

*Number of interviewees considering the condition relevant are shown in parentheses behind the text. Factors are presented in the order of importance.
- No comments were made

There were also distinct answers in the categories compared to monitoring: choice of internal audit topic, guiding instead of monitoring based on internal audit findings and additional contributing factors with regard to the flow and distribution of information, utilisation of internal audits and management and organisation of internal audits.

Internal audits have the potential to guide QMS, but it is not certain that this is achieved. Certain conditions under which both propositions are valid (discussed further in section 10.4) emerged from the data. By taking these into consideration guiding of QMS could be achieved. Indicators which would help measure the effect of internal audit activities could also help with finding out whether internal audits can guide QMS.

### 10.3.3 Chi-square tests for the propositions

Chi-square test for the proposition was done to determine whether the answers were dependent on the background (QA or production) of the interviewee. Contingency tables with observed and expected (statistical) quantities of positive and negative opinions about monitoring and guiding QMS with internal audits are shown in Tables 13 and 14, respectively. Chi-square formula (CHITEST) gave a result of 0.912 for monitoring and 0.409 for guiding QMS with the help of internal audits. Both values are lower than the significance level of 0.05 (confidence level 95%). This indicates that the background of the interviewees did not have an influence on the overall opinion about the proposition. Both QA and production seemed to have the same view on internal audits and this is also emphasized by the fact that each sides considered the internal audit to be based on teamwork and openness (see sections 10.1.5 and 10.1.6).

Table 13. 2 X 2 contingency table showing observed (and expected) quantities of positive and negative opinions by QA and production about monitoring QMS with internal audits.

| | Positive | Negative | Opinions |
|---|---|---|---|
| QA | 6 (5.895) | 2 (2.105) | 8 |
| Production | 8 (8.105) | 3 (2.895) | 11 |
| Sum | 14 | 5 | 19 |
| Result from chi-square formula: 0.912 | | | |

Table 14. 2 X 2 contingency table showing observed (and expected) positive and negative opinions by QA and production about guiding QMS with internal audits.

| | Positive | Negative | Opinions |
|---|---|---|---|
| QA | 10 (9.120) | 2 (2.880) | 12 |
| Production | 9 (9.880) | 4 (3.120) | 13 |
| Sum | 19 | 6 | 26 |
| Result from chi-square formula: 0.409 | | | |

10.4 What is required from internal audits for monitoring and guidance of the quality system?

The conditions under which internal audits can be utilised to control (monitor and guide) quality systems were recognised (Table 15). Each condition is investigated and discussed further.

Table 15. Conditions for valid proposition

| **Conditions under which internal audits can be utilised to guide and control QMS** | |
|---|---|
| 1 | Systematic selection of internal audit topics |
| 2 | Guiding and monitoring on the grounds of internal audit findings |
| 3 | Efficient and flexible flow and distribution of information |
| 4 | Better utilisation of internal audits |
| 5 | Good and effective management and organisation of internal audit activities |

10.4.1 Systematic selection of internal audit topics

Diversified selection of internal audit topics and having a comprehensive set of audits during the course of the year were seen as enablers for monitoring and guiding QMS. Audit topics are selected by QA as stated in the standard operating procedure for internal audits. Topic selection is done partly in co-operation with the departments which could suggest audit topics for the annual audit programme. If audit topics were selected to cover widely the whole field of QMS, it was considered to be able to monitor the system. It was also suggested that both strong and weak areas should be

targeted in order to gain a real picture of the QMS. Concerns considering narrow selection of topics and individual audits being too isolated were also expressed.

In addition to the remarks made about monitoring the audited system, a systematic planning of comprehensive set of audits should be done in order to guide QMS with internal audits. This makes sense in a way that internal audits are able to gather information and set focus on areas of interest simply by selecting the audit topic. Therefore, it is important to select the internal audit topics carefully taking into account the previous and planned audits. An external audit finding can guide the selection of internal audit topic.

Risk assessment could be done when selecting the audit topics. The audits would mostly focus on weaknesses and the most important operations with regard to quality (even if these are considered strong). Also the audit frequency of the topic could be considered by assessing the risks involved and the importance and state of the audited field. This kind of risk-based selection is widely used in pharmaceutical industry and also by the regulatory authorities (Jeronic 2010, Skubch and Zimmer 200).

As an interpretation of results, topic selection can be understood as consisting of three different stages. These stages are compiled in Figure 40 and can also be arranged to resemble the Plan-Do-Study-Act cycle. Stage one is the planning stage where the annual internal audit programme is formed as topics and scope is designed. Stage two is the preparation stage as internal audit agenda for individual internal audits is prepared and detailed plan of what is going to be looked at during internal audits is formed. At this stage it is important to communicate this agenda to participants. Stage three consists of evaluating internal audit report and findings (What kinds of findings were found and are these significant in regard to QMS).

Choice of the next year`s internal audit topics can be partially based on these findings. Estimation of the need for next audit in the same field or other internal audit topics can be done. Even risk analysis concerning what should be followed up and what is under control can be done at this point.

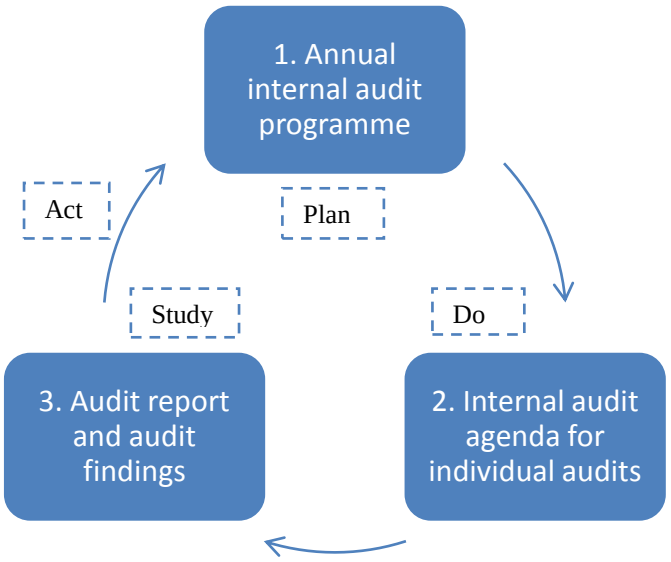


Figure 40. Internal audit topic selection.

### 10.4.2 Monitoring and guiding QMS on the grounds of internal audit findings

Arguments supporting the monitoring of QMS on the grounds of internal audit findings were based on internal audits bringing forth information proactively about own systems and activities not gained elsewhere. Identification of places for improvement and finding out whether or not procedures and instructions are being followed were seen as ways to monitor QMS. It is understood that by monitoring performance, information is gained about the QMS (Saraph et al. 1989). Multiple internal audit findings could give signals about the state of QMS more reliably. It was also discussed that one isolated signal could also tell a lot about the QMS, if it was communicated effectively throughout the organisation and investigated further. For example if a lack in documentation was discovered, it was assumable that this lack could be found also elsewhere within the QMS. By checking documentation based on one finding could have major impact on giving information and monitoring the entire QMS in regard to the audited field together with effective communication. In this way the effects of one single finding could have more far-reaching outcomes than expected.

Correction of procedures based on internal audit findings was seen as a way to control and guide operations to a wanted direction. This way guiding of QMS on the grounds of internal audit findings could be achieved. Also by identifying and implementing improvements, change for better could be achieved. Totally new and even unexpected information can be gathered with internal audits. Corrective or even preventive action taken to these unexpected findings could control the QMS in a manner, which could not be achieved in other ways.

The main concern with both monitoring and guiding was that information gained from internal audits and the findings are too small-scale and detailed to be linked to the QMS. It was expressed that some areas are harder to inspect in the first place and therefore it may be harder to gain "fixable" findings. This means gaining findings where the root cause of the problem can be identified and the problem can be corrected. Some of the causes for findings can be quite complex and interlocking with other activities. Clear definition and understanding of processes can help also with auditing. Internal audits were found suitable to monitor and guide actions. It was expressed that it is more challenging to guide systems than actions. Reasoning behind this might be that systems are more complex and harder to define than individual activities. It was also stated that external audits and quality system audits might have bigger impact than internal audit findings on monitoring and guiding QMS, since these audits are more comprehensive and more focused on the system than on the individual activities or parts of a process.

An interesting trend emerged from the interviews. It was noted that the current internal audit process worked quite well with minor findings, which could be corrected within set timeframes by the department in question itself. In the case of major findings which often demanded commensurate corrective actions, internal audit process was not able to correct all of the findings due to different reasons. Especially findings and actions, which required decision making from several different departments and/or financial input were considered challenging. At the same time, major findings and actions were considered to have more impact and a long-term benefit on the improvement of processes and QMS compared to the minor findings and actions. Possible ways to improve the internal audit process with major findings was discussed. It was suggested

that change management, identification and correction of the root cause of the finding, dividing comprehensive problems into pieces and dealing with these one-by-one, co-operation between departments and experts, handling of corrective actions more sharply, effective communication, and informing the top management could improve the internal audit process with major findings. In addition, some internal audit findings should be approached with the aim of development of operations not just correction of operations. It was also recognised that the aim of the audit process should also be to prevent future findings by learning from current internal audit findings and their correction.

### 10.4.3 Efficient and flexible flow and distribution of information

Flow and distribution of information was considered valuable in monitoring the QMS. Auditor`s role as information distributor during the audit and distribution of information to top management regarding the internal audit findings was mentioned in both cases. In the case of guiding the QMS with the help of internal audits, the efficient and flexible flow and distribution of information was emphasized even more. Information to top management regarding the internal audit findings could aim to redirect resources to the weaker areas. Communication about corrective actions towards top and bottom were also mentioned. This way actions to findings could be more effectively conducted. Also auditor`s role as active distributor of the latest information during the audit itself was referred to.

### 10.4.4 Better utilisation of internal audits

Utilisation of internal audits was discussed in chapter 10.2. Better utilisation was also mentioned to be one of the conditions under, which both of the hypotheses would be valid. It was expressed that enough time to form a recap and reflect on the internal audit findings from multiple individual audits should be given to be able to monitor QMS. Internal audits have also the opportunity to guide QMS, if utilised more effectively. Internal audits may guide the culture of company and work habit and even enforce or maintain QMS by keeping it up-dated with the changing environment.

### 10.4.5 Good and effective management and organization of internal audit activities

The overall management and organisation of internal audits was mentioned to be one of the enablers to utilise internal audits to guide QMS. This includes the selection of internal audit topics and flow of information, which were already recognised as conditions for a valid proposition in both cases. Good and effective management also includes the concept of effective internal audit and organising time and resources for the execution of internal audit activities and the implementation of corrective actions based on internal audit findings.

Reasons for why exactly these five factors were regarded as conditions to control QMS were considered. Systematic selection of internal audit topics ensures that internal audits are focused on important matters relating to the QMS from the beginning of the process. Findings are the most important outcome of internal audit process as these may reveal the condition of the audited system and the audit process itself. Corrective actions in response to these findings are also crucial, as these corrections can improve the audited system. Better utilisation of internal audits might lead to efficient use of the resources. Efficient and flexible flow and distribution of information enables smooth internal audit process and makes people aware of the strengths and weaknesses of their own processes. Also the management of internal audit activities should be focused on. Internal audits are a significant part of QMS and to be able to develop QMS, internal audits need to be developed as well.

From the analysis of well functioning and challenging areas, it can be seen that the preparation phase and the on-site activities of internal audit are already considered to be functioning especially well. This might be the reason, why these factors are not considered here, though these areas are essential for a functioning audit. Taking corrective action was mentioned as a challenge. This was not directly set as a condition, but this phase has an important role in implementing change, improvements and corrections as a response to internal audit findings, which are used to monitor and guide operations and QMS.

# 11 QUALITY AND RELIABILITY

Assessment of the quality of qualitative work differs from the assessment of quantitative research. The conventional positivist way to consider the quality of a quantitative research findings and the method is to evaluate its validity, reliability and objectivity (Zhang and Wildemuth 2009). These set of criteria for quality can also be applied to qualitative research to some aspect. Because of the different approach (objective, data collection, analysis) in qualitative research, this is not always a suitable way to describe the quality of qualitative work and also other aspects need to be considered.

The quality of qualitative research is often described as the trustworthiness of findings, which consists of the estimation of quality of the work based on its credibility, transferability, dependability, strengthening and confirmability (Hoepfl 1997, Kylmä and Juvakka 2007, Thomas 2003, Zhang and Wildemuth 2009). These aspects are used in the assessment of the quality of this work. Credibility and transferability describe the validity of the work internally and externally, respectively. Dependability addresses the reliability of qualitative work. Strengthening means comparing results to pre-existing results and finding parallels, which can confirm recent research and confirmability takes into account the objectivity of the work.

## 11.1 Credibility

Research credibility is increased, if the studied phenomena is described precisely and truthfully based on the interviewee`s point of view. Credibility can be improved by triangulation, feedback and by transcribing the data accurately and interpreting data correctly.

Interviews were recorded and transcribed. Recording of the interviews was thought to increase the credibility of the research and making the gathering of data more efficient. The duration of interviews was also reduced and interviewee´s valuable time could be spared. Interviewer could also concentrate entirely on asking questions and responding

to interviewees answers as note taking was not hindering this process. More accurate and consistent data could also be collected as interviews could be transcribed verbatim and the interviewer could go back and listen to or look at the answers more closely. Also the creation of a coding frame supported consistent data interpretation as it supported the categorization of data.

Data interpretation was done based on the data in the transcripts and the formation of an index frame where data was gathered. Transcriptions and index frame was studied several times to gain comprehensive and correct interpretation of the data. This process was also described in detail. Misinterpretation of data could take place in two separate stages and this was paid attention to. These stages were the interpretation of how to categorize the data and the final interpretation of the categorized data. Categorization of the data into the index frame was double-checked. At the interpretation stage, feedback from participants and users of the research findings could have taken place. This was not done in this research, but this would be a method to increase the credibility as the interviewees are the ones, who could assess the credibility of the interpretations and made conclusions. Direct quotes were used to support the interpretation of data and these also reveal the opinions of the interviewees for the reader.

Triangulation (combination of different study methods, sources of information or ways to collect data e.g. interview, observation and survey) can give a more comprehensive analysis of the data. This was not done in this study. Observation of internal audit activities or a survey study to larger sample could have been executed together with interviews to increase the credibility (validity) of this work.

The inexperience of the researcher might affect the credibility of the research in a negative way. Data collection and the analysis of data are the most vulnerable stages of the research as the gathered data is sensible to researcher`s choices and handling of data. A journal of the progress of this work and the used methods was held and memo`s were kept considering the contents of the interviews. Methods used in research and data collection were also explained in detail to show how the data was interpreted. This in turn increases the credibility. The choice of semi-structured interview form eased

somewhat the data collection and analysis (especially the coding phase) compared to other types of interviews. Pilot interviews increased the credibility of this work. Interviewer gained a change to practice interviewing skills in these pilots and the most important tool, the interview questions, could be fine-tuned.

Also any prior assumptions may affect the results and these need to be aware of. The literature review was done in forehand and it was important not to be too much influenced of others work and to keep an open mind as doing research. Leading questions were also avoided during interviews to not bias the data collection. Attention was paid to both positive and negative cases. Contradictive explanations in the data were investigated before making further assumptions (deviant case analysis).

Saturation of data was achieved. This was monitored in this work to find out whether enough interviews were held to collect valid amount of data. Data saturation is reached when new points are no longer raised in the interviews (Hämeen-Anttila and Katajavuori 2008). Reaching this point increased the credibility of this work in a similar way that the sample size increases the validity of a quantitative research.

Data was mostly analysed qualitatively. Quantitative data analysis was done to support the analysis. Also some statistical testing was done to identify the influence of the interviewee`s background on the answers. This statistical testing was found difficult because of the small sample size and small amount of numerical data. Also other tests were considered, but after careful considerations chi-square test was used to test the data for independence. Other deliberated tests were Yates correction for continuity, G test, multinomial test, Fisher`s exact test and Bayesian hypothesis selection. By combining different methods to analyse the data, triangulation of the analysis phase is achieved and this may increase the correct interpretation of data and in turn increases the credibility and trustworthiness of this work.

## 11.2 Transferability

Transferability describes if similar conclusions could be reached in other populations. This study was done in pharmaceutical industry, but it handled a more general subject, namely QMS and internal audits. Management systems can be part of any production and service industry. In this sense this study could offer information and be valid also in other fields of business outside of pharmaceutical industry. Pharmaceutical industry is heavily regulated and has complex operations and systems and is highly safety oriented. Similar industry, such as food, automotive and aviation industry might have close to the same type of requirements for QMS as in pharmaceutical industry. Even the transferability of this work to other pharmaceutical industry might be questioned. This study only reflects the opinions made in Orion`s site at Espoo. It considers some of the functions (e.g. harmonisation and cooperation between sites) at the other sites (in Kuopio and Turku) as well. And these results could be partially transferable to these sites.

Other studies concerning internal audits have mainly been survey studies (Elliot et al. 2007, Jeronic 2010) or case studies (Beckmerhagen et al 2003, Kausek 2008, Morris 2008), done on the process of internal audit itself (e.g. Karapetrovic and Wilborne 2000 and 2001, Beckmerhagen et al. 2004, Elliot et al. 2007) and on internal audit as a mean to gain compliance and to continuously improve systems (Beecroft 1996, Kaye and Anderson 1999). Some of the results were confirmed by similar findings in other studies and these are discussed in chapter 10.

It was thought, whether or not it is possible for other researchers to confirm these results and reach similar conclusions. The replication of this study is made possible, due to the detailed analysis method. The analysis phase was made transparent by describing the different stages of this work in detail. The reached conclusions were traceable, because of the carefully designed coding and index frame. Segments of texts were coded in a way that allowed tracking of the original opinions from the made conclusions. This increased the transparency of reached conclusions. By explaining the role of deviant cases, checking the data thoroughly several times and describing the environment the

research was done in the main research findings can be transferable to similar environments.

Relevance of the quantitative research considers generalization of the findings and creating new information about the researched area (Hämeen-Anttila and Katajavuori 2008, Mays and Pope 2000). It was not the aim of this qualitative research to gain generalised findings. Purposive sampling method and the small sample size could not lead to generalized findings. In this case, the aim was to create deeper knowledge about the research topic and this could be done by choosing the interviewers who had most insight and knowledge about the topic. In this way the relevance of research was increased, as more detailed information explaining the studied phenomenon could be gained.

The pharmaceutical field is of its own kind so it would be hard to generalize or use these findings outside of pharmaceutical industry. It can be concluded that these findings are relevant and representative internally for Orion. Comparison to previous research from different fields showed similar results. This also increased the relevance of the research.

## 11.3 Dependability

Dependability relates to the reliability of this research. This work was done in pharmaceutical field, which has some typical features. The pharmaceutical industry and its environment are in constant change. Though the manufacturing environment needs to be strictly controlled, over time the regulations change and technology is improved and the industry needs to adapt to these changes. The context in which this research was made is also affected by change. If this research would be duplicated after few years it could result in different conclusion due to the fact that improvements, developments and changes in the environment affect also the conditions we work in. It would be important to figure out how these changes have affected these results. Also the refocus, which these research results may cause, might be shifted to the more challenging areas. As

these are dealt with, they no longer possess challenges but may become strengths and completely new areas may emerge, which are more challenging.

## 11.4 Strengthening and confirmability

Comparison with previous findings and replication of the research in the future are methods, which may increase the trustworthiness of a research. Comparison of the results of this work with previous findings and ideas presented in the literature review were done. Additional literature research was done after the interviews were analysed and interpret to find similar or opposing conclusions, which could support or help analyse the results more fully. There is little research done on the monitoring and guiding QMS with internal audits in the pharmaceutical field, so literature was also searched from other fields. Also possible suggestions for action (based on results) were found from literature.

When it comes to confirmability of the work, interviewees` opinions were objectively presented and interpreted. Also own opinions were presented but these were kept separate from interviewees` opinions. Conclusions were based on both literature and results found in this work.

# 12 CONCLUSIONS

Based on this work internal audits can monitor and have the potential to guide QMS under certain conditions. Internal audit topics need to be systematically selected, QMS needs to be monitored and guided based on the internal audit findings, flow and distribution of information needs to be efficient and flexible, and internal audits should be better utilised and managed.

Monitoring of the QMS can be looked at as the starting point to guide QMS. In order to comprehensively control (monitor and guide) QMS, it is not enough to just utilise internal audits more fully. The whole process of internal auditing needs to be focused (setting a goal of the audit) on gaining valuable information about QMS and linking the individual audits and findings to consider the whole QMS. It starts from the planning (selection of topics), moves on to the on-site activities and to actions based on the audit findings. Also signals and valuable information about QMS can be gained with the follow-up, which can be used to ensure that corrective actions have been done and evaluate how these have affected the audited system. In total this follow-up may indicate, whether internal audits have taken the audited system towards right direction. As internal audits can be used to control QMS and QMS controls the companywide quality, an overall effect on quality can be achieved.

Some concluding remarks and recommendations can be made based on this work with regard to better utilisation of internal audits with QMS. Isolated individual internal audits need to be linked to QMS to gain a comprehensive picture of the QMS`s status. An example of possible linkages between different internal audit subjects or different kinds of findings made is shown in Figure 42. By categorising the audit topics or findings and linking them to QMS, all the individual audits can contribute to the monitoring and guiding of QMS.

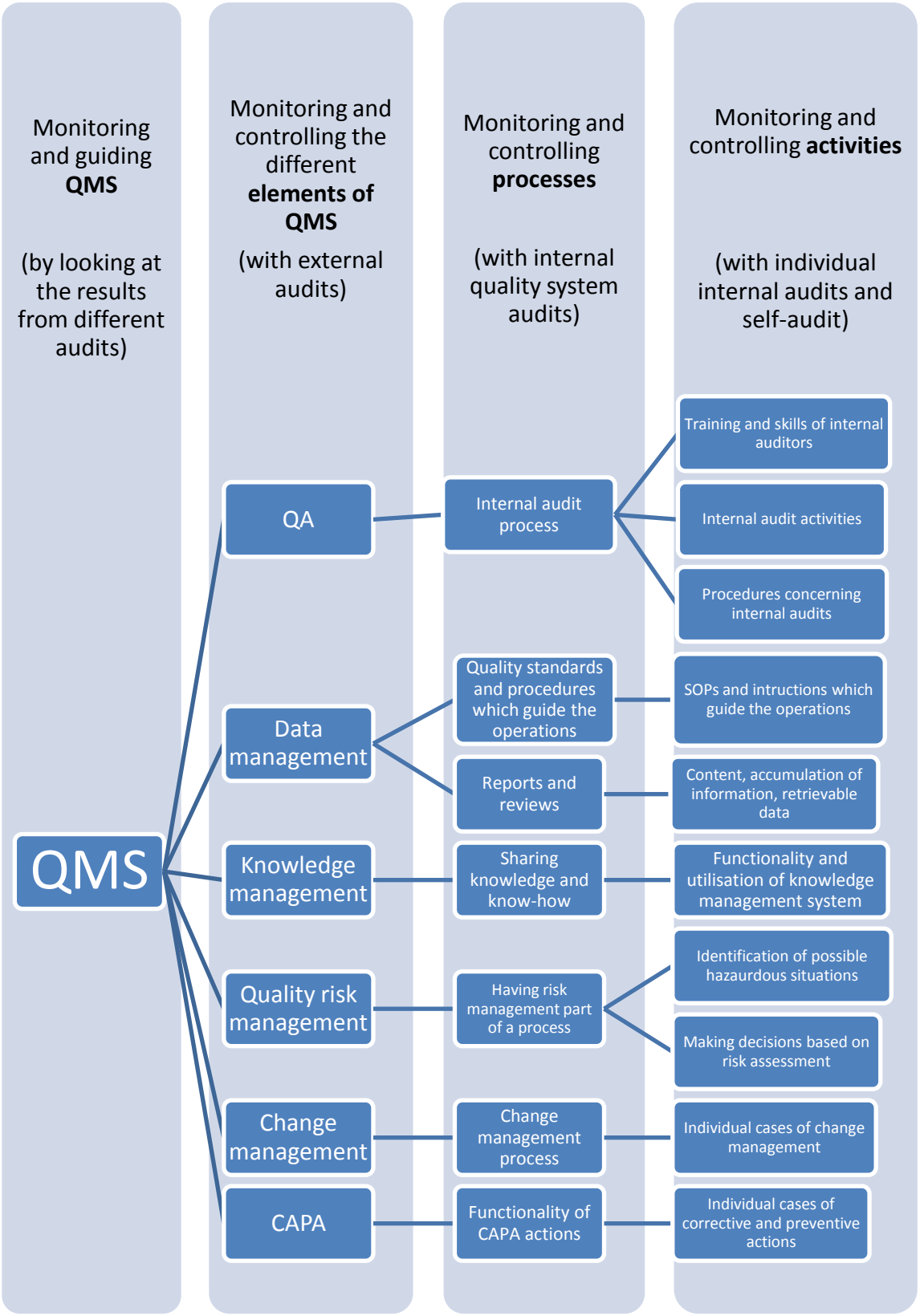


Figure 42. Monitoring and guiding QMS with the help of internal audits.

As can be seen from the Figure 42, the findings made on the far right side of the figure can be very detailed in nature and by linking these to wider concepts it can contribute to give information about the QMS. As mentioned earlier (in the part of utilisation of internal audits), a single internal audit finding can be looked at as a representative sample from a large population and give information about the status of QMS. Many different types of audits can be utilised to gain information about QMS during the course of the year.

Combining information from individual internal audits, QMS audits and external audits throughout the organisation and also from other sources (product quality review, CAPA) is important. One should not rely only on one information source (e.g. internal audit) even though a single finding could give information about the whole QMS when it is communicated effectively throughout the organisation and the topics are selected with care. Getting confirming information is important as this tells also about the functionality of the audit process itself and can help to monitor and guide QMS.

Information flow in regard to internal audit findings needs to be flexible and effective. Better communication between departments and sites, updated and easily available recommendation tables where one could see what has been audited on other departments and sites and what kind of findings were made, and recommendation about what kind of areas should be focused on in the departments. On the basis of this, self-audit could be made to find out if same findings can be found on own department and this could be reported upwards and an internal audit could be held if wider problems occur for further investigation of problems. This way one single internal audit could result have far-reaching effects in the whole system. Harmonising procedures and practices should also be a top priority as this eases the monitoring and controlling of these processes.

Tour of the audited facilities was mentioned by the interviewees as a good way to conduct audit activities on site. These could also be arranged as pre-audit meetings before the opening meeting of an internal audit. This way these would serve as a good way to prepare for the actual audit (Askey and Dale 1994). All this preparation makes

the official audit run more smoothly and on schedule and could also enable smooth flow to corrective action if processes and problem areas are looked into in forehand.

Training of employees is a matter which could be developed systematically. Working in three or even five shifts sets challenges for an effective training of staff. Tools to manage this should be looked into e.g. taped training sessions which could be stored and retrieved from a document management system dedicated to training material. This way training sessions are made more flexible.

Development of tools to aid better utilisation of internal audits in the control of QMS can be suggested based on this work. Further research on the development of these tools and their implementation is needed. Further investigation is also needed to find out how to record and measure the effects of internal auditing, especially when it comes to guiding QMS with internal audits.

## 13 REFERENCES

Adam EE: Alternative quality improvement practices and organization performance. J Oper Manag 12:27–44, 1994

Adis W: Pharmaceutical riks control systems. Commun IIMA 8:1–9, 2008

Alic M, Rusjan B: Contribution of the ISO 9001 internal audit to business performance. Int J Qual Reliab Manag 27:916–937, 2010

Andersson R, Eriksson H, Torstensson H: Similarities and differences between TQM, six sigma and lean. The TQM Magazine 18:282–296, 2006

Antony J: Some pros and cons of six sigma: an academic perspective. The TQM Magazine 16:303–306, 2004

Antony J, Banuelas R: Key ingredients for the effective implementation of Six Sigma program. Measuring Business Excellence 6:20–27, 2002

Aravindan P, Devadasan SR, Selladurai V: A focused system model for strategic quality management. Int J Qual Reliab Manag 13:79–96, 1996

Arayne MS, Sultana N, Zaman MK: Historical incidents leading to the evolution of good manufacturing practice. Accredit Qual Assur 13:431–432, 2008

Arnheiter ED, Maleyeff J: The integration of lean management and Six Sigma. The TQM Magazine 17:5–18, 2005

Arter DR: Quality audits for improved performance. 3rd edition. ASQ Quality Press, Milwaukee 2003

Askey JM, Dale BG: Internal quality management auditing: an examination. Manag Audit J 9:3–10, 1994

Beamon BM: Measuring supply chain performance. Int J Oper Prod Manag 19:275–292, 1999

Beckmerhagen IA, Berg HP, Karapetrovic SV, Willborn WO: Auditing in support of the integration of management systems: a case from the nuclear industry. Manag Audit J 18:560–568, 2003

Beecroft GD: Internal quality audits-obstacles or opportunities?. Train Qual 4:32–34, 1996

Bernardo M, Casadesus M, Karapetrovic S, Heras I: An empirical study on the integration of management system audits. J Clean Prod 18:486–495, 2010

Biazzo S, Bernardi G: Process management practices and quality systems standards: Risks and opportunities of the new ISO 9001 certification. Bus Process Manag J 9:149–169, 2003

Borkar MM: GMP Assessment: A Tool To Evaluate Leadership. J GXP Compliance 11:10–17, 2006

Bou-Llusar JC, Escrig-Tena AB, Roca-Puig V, Beltrán-Martín I: To what extent do enablers explain results in the EFQM excellence model?: An empirical study. Int J Qual Reliab Manag 22:337–353, 2005

Buecker J, Tuttle J: Change Management Systems in the Pharmaceutical Industry. Pharmaceut Eng 6:1–6, 2002

Camilli G, Hopkins KD: Applicability of Chi-square to 2 X 2 contingency tables with small expected cell frequencies. Psychol Bull 85:163–167, 1978

Carter-Hamm B, Vinson G: Facilitating client audits: The contract laboratory perspective. BioPharm 15:12–16, 2002

Chan FY, Willborn W, Xiao H, Li H: Research report: an expert system for quality management auditing. Int J Qual Reliab Manag 10:65–72, 1993

Cusumano MA: The Limits of " Lean". Sloan Manage Rev 35:27–32, 1994

Crombie IK, Davies HTO. Missing link in the audit cycle. Qual Health Care 2:47–48, 1993

Delucchi DL: The use and misuse of the chi-square test: Lewis and Burke revisited. Psychol Bull 94:166–176, 1983

Deming WE: Out of the Crisis. MIT Press, Massachusetts 1982

Deming WE: The new Economics for Industry. MIT Press, Massachusetts 1994

DeVito J, Jagota N, Vudathala G, Tammara V: Preparation for a Regulatory Pre-Approval Inspection. Clin Res Regul Aff 23:97–123, 2006

DiCicco-Bloom B, Crabtree BF: The qualitative research interview. Med Educ 40:314–321, 2006

Dimasi JA: The value of improving the productivity of the drug development process: faster times and better decisions. Pharmacoeconomics 20:1–10, 2002

Drakulich A: All Roads Now Lead to Quality Systems. Pharm Technol 32:42–7, 2008

Edwards AG: Quality Systems for Drugs and Biologics. Pharm Technol 32:60–75, 2008

EFQM Excellence Model. Laatukeskus Excellence. EFQM publications, Finland 2010

Elliott M, Dawson R, Edwards J: An improved process model for internal auditing. Manag Audit J 22:552–65, 2007

EN ISO 9000: 2005, Quality management systems - Fundamentals and vocabulary (ISO 9000:2005)

EN ISO 19011:2002, Guidelines for quality and/or environmental management systems auditing (ISO 19011:2002)

EU guidelines to Good Manufacturing Practice, Introduction. The rules governing medicinal products in the European Union (Eudralex), Volume 4, 2010

EU guidelines to Good Manufacturing Practice, Quality Management. The rules governing medicinal products in the European Union (Eudralex), Volume 4, Chapter 1, 2008

EU guidelines to Good Manufacturing Practice, Quality Control. The rules governing medicinal products in the European Union (Eudralex), Volume 4, Chapter 6, 2006

EU guidelines to Good Manufacturing Practice, Complaints and product recall. The rules governing medicinal products in the European Union (Eudralex), Volume 4, Chapter 8, 2006

EU guidelines to Good Manufacturing Practice, Self-inspection. The rules governing medicinal products in the European Union (Eudralex), Volume 4, Chapter 9. Accessed from the Internet 14.12.2010 http://ec.europa.eu/health/files/eudralex/vol-4/pdfs-en/cap9_en.pdf

Fadzil FH, Haron H, Jantan M: Internal auditing practices and internal control system. Manag Audit J 20:844–66, 2005

FDA/CDER: Guidance for industry – Quality systems approach to pharmaceutical CGMP regulation, September 2006

Feldman S: Quality assurance: Much more than testing. Queue 3:27–29, 2005

Forker LB, Vickery SK, Droge CLM: The contribution of quality to business performance. Int J Oper Produc Manag 16:44–62, 1996

Fowler J: STEP for data management, exchange and sharing. Technology Appraisals, Great Britain 1995

Franco-Santos M, Kennerley M, Micheli P, Martinez V, Mason S, Marr B, Gray D, Neely A: Towards a definition of a business performance measurement system. Int J Oper Produc Manag 27:784–801, 2007

Garvin DA: Quality on the line. Harv Bus Rev 61:65–75, 1983

Garvin DA: Product quality: An important strategic weapon. Bus Horizons March-April:40–43, 1984

Garvin DA: What does product quality really mean? Sloan Manage Rev 26:25–45, 1984

Gliner JA, Morgan GA, Harmon RJ: The chi-square test and accompanying effect size indices. J Am Acad Child Adolesc Psychiatr 41:1510–1512, 2002

Goldberg Y, Shmilovici A: An expert system approach for quality assurance auditing. Int J Adv Manuf Tech 26:415–419, 2005

Gupta P: Inspections vs. Audits. PC FAB 23:76–77, 2000

Gupta P: Beyond PDCA- a new process management model. Qual Prog 39:45–52, 2006

Hattemer-Apostel R: Quality assurance, quality control and audit. In Principles and practice of pharmaceutical medicine, p. 159–178, 2nd edition. John Wiley & Sons, Chichester 2007

Hoepfl MC: Choosing Qualitative Research: A Primer for Technology Education Researchers. J Technol Educ 9:47–63, 1997

Hung Y-C, Huang S-M, Lin Q-P, Tsai M-L: Critical factors in adopting a knowledge management system for the pharmaceutical industry. Ind Manag Data Syst 105:164–183, 2005

Hämeen-Anttila K, Katajavuori N: Yhteiskunnallinen lääketutkimus – ideasta näyttöön. Esa Print, Tampere 2008

ICH: About ICH. Accessed from the Internet 14.12.2010: http://www.ich.org/home.html

ICH: Q8 Pharmaceutical development, step 4 version, August 2009

ICH: Q9 Quality risk management, step 4 version, November 2005

ICH: Q10 Pharmaceutical quality system, step 4 version, June 2008

Ishikawa K: Guide to quality control. Asian productivity organisation, Tokyo 1976

ISO: The ISO survey of certifications 2007, 2008. Accessed from the Internet 27.1.2011: http://www.iso.org/iso/survey2007.pdf

Jeronic B: Improved utilization of self-inspection programs within the GMP environment - A quality risk management approach. J GXP Compliance 14:84–96, 2010

Jones AB: Principles in quality assurance. Part 1. Sink or swim. Qual Assur J 6:219–225, 2002

Jonker J, Karapetrovic S. Systems thinking for the integration of management systems. Bus Process Manag J 10:608–615, 2004

Juran JM: Juran on Quality by Design: the new steps for planning quality into goods and services. The free Press, New York 1992

Juran JM: The quality trilogy – A universal approach to managing for quality. Qual Prog August:19–24, 1986

Karapetrovic S: Quality assurance and effectiveness of audit systems. The Int J Qual Reliab Manag 17:679, 2000

Karapetrovic S: Strategies for the integration of management systems and standards. The TQM Magazine 14:61–7, 2002

Karapetrovic S, Willborn W: Generic audit of management systems: fundamentals. Manag Audit J 15:279–94, 2000

Karapetrovic S, Willborn W: Audit system: concepts and practices. Total Qual Manage 12:13–28, 2001(2001a)

Karapetrovic S, Willborn W: Audit and self-assessment in quality management: comparison and compatibility. Manag Audit J 16:366–77, 2001 (2001b)

Karapetrovic S, Willborn W: Self-audit of process performance. Int J Qual Reliab Manag 19:24–45, 2002

Kaye M, Anderson R: Continuous improvement: the ten essential criteria. Int J Qual Reliab Manag 16:485–509, 1999

Kimmel HD: The relationship between chi square and size of sample: the general case. J Appl Psychol 40:415–416, 1956

Klefsjö B, Wiklund H, Edgeman RL: Six Sigma seen as a methodology for total quality management. Measuring Business Excellence 5:31–5, 2001

Kueng P: Process performance measurement system: A tool to support process-based organizations. Total Qual Manage 11:67–85, 2000

Kvale S: Interviews: An introduction to qualitative research interviewing. Sage publications, Thousand Oaks California 1996

Kylmä J, Juvakka T: Laadullinen terveystutkimus. Edita Prima Oy, Helsinki 2007

Lau R, Anderson C: A three-dimensional perspective of total quality management. Int J Qual Reliab Manag 15:85–98, 1998

Lee TY, Leung HKN, Chan KCC: Improving quality management on the basis of ISO 9000. The TQM Magazine 11:88–94, 1999

Lewis D, Burke CJ: The use and misuse of the chi-square test. Psychol Bull 46:433–489, 1949

Liu TD, Xu WX: A review of web-based product data management systems. Comput Ind 44:251–62, 2001

Low SP, Omar HF: The effective maintenance of quality management systems in the construction industry. Int J Qual Reliab Manag 14:768–90, 1997

Lubit R: Tacit knowledge and knowledge management: The keys to sustainable competitive advantage. Organ Dyn 29:164–78, 2001

Mann R, Kehoe D: Factors affecting the implementation and success of TQM. Int J Qual Reliab Manag 12:11–23, 1995

Markovitz D: GXP – Quality, responsibility, integrity and accountability. J GXP Compliance 14:20–22, 2010

Mays N, Pope C: Qualitative research in health care: Assessing quality in qualitative research. Brit Med J 320:50–52, 2000

McAdam R, Barron N: The role of quality management in pharmaceutical development: clinical trials analysis. Int J Health Care Qual Assur 15:106–23, 2002

McConnell J, Nunnally BK, McGarvey B: The Forgotten Origins of Quality by Design. Journal of Validation Technology 16:30–4, 2010

McNamara C: General guidelines for conducting interviews. Accessed from the Internet 11.1.2011: http://managementhelp.org/evaluatn/intrview.htm

Nagy AL, Cenker WJ: An assessment of the newly defined internal audit function. Manag Aud J 17:130–7, 2002

Najmi M, Kehoe DF: An integrated framework for post-ISO 9000 quality development. Int J Qual Reliab Manag 17:226–58, 2000

Naveh E, Marcus AA: When does the ISO 9000 quality assurance standard lead to performance improvement? Assimilation and going beyond. IEEE T Eng Manage 51:352–63, 2004

Neely A, Gregory M, Platts K: Performance measurement system design: A literature review and research agenda. Int J Oper Prod Manag 15:80–116, 1995

Nollau B: Forming a Partnership Between IT and QA. J GXP Compliance 14:60, 2010

Onodera K: Effective techniques of FMEA at each life-cycle stage. In Proceedings of the Annual Reliability and Maintainability Symposium, pp. 50–56, 2002

Percy B: Change management and quality: ensuring a change for the better. RAJ Pharma July:411–414, 2010

Pharmaceutical quality group: Pharmaceutical auditing, monograph no.5. Institute of quality assurance. 2nd edition, Yorkshire 2001

PIC/S: Explanatory notes for pharmaceutical manufacturers on the preparation of a site master file, Annex 1. January, 2011

Pirsing RM: An inquiery into morals. Bantam Books, New York 1992

Pope C, Ziebland S, Mays N: Qualitative research in health care: Analysing qualitative data. Brit Med J 320:114–116, 2000

Poska R: Self inspection and its potential benefits via ICH Q9 - An interview with Kevin O`Donnell, Ph.D, Irish Medicines Board. Journal of Validation Technology 12:15–24, 2008

Probitts J: Auditing in the manufacturing environment. Qual Assur J 4:193–6, 2000

Rajendran M, Devadasan SR: Quality audits: their status, prowess and future focus. Manag Audit J 20:364–82, 2005

Ramly EF, Ramly ES, Yusof SM: Effectiveness of quality management system audit to improve quality performance - A conceptual framework. In The Fifth International Conference on Quality and Reliability (ICQR 2007), p. 26–31, 2008

Reeves CA, Bednar DA: Defining quality: alternatives and implications. Acad Manage Rev 19:419–45, 1994

Ricci MT, Fraser HE: From quality by inspection to quality by design: A roadmap for success. Pharm Technol 22–27, 2006

Rodriguez J: How To Prepare For A Systems-Based Inspection-Understanding FDA's Risk-Based Inspections Approach. J GXP Compliance 9:72–87, 2005

Rönninger S, Malcolm H: A Risk-Based Approach to Scheduling Audits. PDA J Pharm SciTech 63:575, 2009

Saraph JV, Benson PG, Schroeder RG: An Instrument For Measuring The Critical Factors Of Quality. Decision Sci 20:810–829, 1989

Sawyer LB, Dittenhofer DA, Scheiner JH: Sawyer's Internal Auditing: The Practice of Modern Internal Auditing. 5th edition. Institute of Internal Auditors. USA, 2003

Schindel-Bidinelli EM: Quality assurance--adhesive bonding audits: New approaches to quality assurance and to QA monitoring audits. Int J Adhes Adhes 16:33–7, 1996

Schröder MJA, McEachern MG: ISO 9001 as an audit frame for integrated quality management in meat supply chains: the example of Scottish beef. Manage Aud J 17:79–85, 2002

Sebastianelli R, Tamimi N: How product quality dimensions relate to defining quality. Int J Qual Reliab Manag 19:442–453, 2002

Sharp J: Quality in the Manufacture of Medicines and Other Healthcare Products. Pharmaceutical Press, London 2000

Shepherd C, Günter H: Measuring supply chain performance: current research and future directions. Int J Prod Perform Manag 55:242–258, 2006

Silverman D: Doing qualitative research. 2nd edition. Cromwell Press Ltd, Great Britain 2007

Singels J, Ruel G, van de Water H: ISO 9000 series-Certification and performance. Int J Qual Reliab Manag 18:62–75, 2001

Skubch N, Zimmer T: Long-term QA trends in pharma. Pharmaceut Tech Eur 21:26–30, 2009

Snee R: Quality by Design—four years and three myths later. Pharm Process 2:14–6, 2009

Taguchi G, Clausing D: Robust quality. Harv Bus Rev 68:65–75, 1990

Talbot J, Nilsson B: Pharmacovigilance in the pharmaceutical industry. Br J Clin Pharmacol 45:427–31, 1998

Taormina T: Successful Internal Auditing to Iso 9000. Prentice Hall PTR, Portland OR 1999

Tarí JJ: Components of successful total quality management. The TQM magazine 17:182–94, 2005

Taylor W, Wright G: A longitudinal study of TQM implementation: factors influencing success and failure. Omega 31:97–111, 2003

Terziovski M, Power D, Sohal AS: The longitudinal effects of the ISO 9000 certification process on business performance. Eur J Oper Res 146:580–595, 2003

Terziovski M, Samson D, Dow D: The business value of quality management systems certification. Evidence from Australia and New Zealand. J Oper Manage 15:1–18, 1997

Texeira-Quirós J, Almaça JA, Fernandes-Justino MR: How quality affects the bottom line?: A literature review. Intangible capital 6:258, 2010

Vinten G: Putting ethics into quality. The TQM Magazine10:89–94, 1998

Turner DW: Qualitative interview design: A practical guide to novice investigators. Qual Rep 15:754–760, 2010

Van Arnum P: ICH Q10: A Recipe for the Product Life Cycle. Pharmaceut Tech 31:50–7, 2007

Vogel D: The globalization of pharmaceutical regulation. Governance 11:1–22, 1998

Wang RY: A product perspective on total data quality management. Commun ACM 41:58–65, 1998

WHO: Self-inspection and quality audits. WHO Technical Report Series No. 908, Annex 4, 2003

WHO: Application of Hazard Analysis and Critical Control Point (HACCP) methodology to pharmaceuticals. WHO Technical Report Series No. 908, Annex 7, 2003

Williamson A, Rogerson JH, Vella AD: Quality system auditors` attitudes and methods: A survey. Int J Qual Reliab Manag 13(8):39–52,1996

Wilson DD, Collier DA: An empirical investigation of the Malcolm Baldrige National Quality Award causal model. Decision Sci 31:361–83, 2000

Wong KY: Critical success factors for implementing knowledge management in small and medium enterprises. Ind Manag Data Syst 105:261–79, 2005

Woodcock J: The concept of pharmaceutical quality. Am Pharmaceut Rev 7:10–5, 2004

Yu LX: Pharmaceutical quality by design: product and process development, understanding, and control. Pharmaceut Res 25:781–91, 2008

Zhang Y, Wildemuth BM: Qualitative analysis of content , Applications of
Social Research Methods to Questions in Information and Library, 2009. Accessed from the Internet 6.4.2011: http://www.ischool.utexas.edu/~yanz/Content_analysis.pdf

Zeithaml VA, Parasuraman A, Berry LL: Delivering quality service: balancing customer perceptions and expectations. The Free Press, New York 1990

APPENDIX 1

The interview schedule

A) Interviewee background information
    1. Tell me about your background.
    2. What kinds of activities are included in your job description?

B) Internal audits from interviewee`s point of view
    3. How do YOU participate in internal audits?
    4. What type of internal audits have you been taken part in?
    5. Shortly describe the course of internal audits from YOUR viewpoint.

C) Internal audit status and development
    6. What is, in your opinion, the goal of internal audit? Is this goal being fulfilled?
    7. What are the three most important features of a functioning internal audit?
    8. What is needed to support these features and get the audit functioning according to its purpose?
    9. What works especially well in internal audits?
    10. What is challenging with internal audits?
    11. What kind of improvements could be made to manage these challenges?

D) Different stages of internal audits in more detail (what kind of impact or meaning these stages have from interviewer`s point of view)
    12. What should be focused on in internal audits?
    13. What kind of skills are important to the auditor/auditee?
    14. How should one prepare for an internal audit?
    15. What kind of findings are made and what is the response to internal audit findings?
    16. How are operations (resulted from audit findings) executed?
    17. How is the follow-up of these actions executed?
    18. How are the audit results presented?

E) Utilization of internal audits in accordance with the development of QMS
    19. What have been the benefits of internal audits?
        -How internal audits have been utilized?
        -How internal audits could be utilized even more?
    20. Can internal audits affect the monitoring or/and guiding of QMS? How?

F) Lastly
    21. Anything to add? Have we gone through the relevant aspects of this topic?

APPENDIX 2

Coding process and coding frame

Coding was done by hand by underlining specific text segments from the raw data. Text segments were given a number (according to the coding frame) which was placed in the margin. If justified, segment of text could be coded into two different categories (piece of text contained two different points or the meaning of these points were strongly linked together). Unconnected or insignificant matters to this research topic were not coded (this was decided by the researcher).

First, half of the interviews were coded (5) and the coding frame was build-up. Then the last half of the interviews (4) were coded according to the coding frame and new codes were created if these were not already found in the coding frame. Saturation level of data was evaluated alongside coding process. New round of coding was done regarding the added codings to the final coding frame.

Identifying marks were created to distinguish between the answers of different individuals and also to be able to take their background into account. These markings were used in the index frame to show where the coded piece of text came from. This way interpretations made based on categorised findings could be traced back to the raw data. This increased the traceability of the analysing method. (The information revealing the true identity of the interviewee was kept separate from the coding lists. Only information, whether the interviewee was from manufacturing or quality assurance, was revealed by the identifying marks). In the index frame colour codes were later added to more easily differentiate between the answers of these two groups. The distribution of answers could be easily glanced over this way. (Further calculations were made, if there seemed to be difference between the opinions of these two groups.)

Table: Identifying marks

| Manufacturing | Quality assurance |
|---|---|
| 1M | 1Q |
| 2M | 2Q |
| 3M | 3Q |
| 4M | 4Q |
| | 5Q |
| Colour code: green | Colour code: red |

All substantial coded texts were given numbers which indicated the category they belonged to in the coding frame. The numbers were given in the order of appearance of the particular category as the coding proceeded. The coding frame “lived” and was developed throughout the coding of every interview. If new categories were coded, the previous interviews were looked through again more closely to find out whether these could be recognized from the text. As the coding of the text proceeded more and more detailed observations were made and the coding frame transformed. Some of the codes were lastly reorganized to contain sub groups which formed the code. Codes were given numbers and the sub codes were given an additional letter attached to this number. The

formation of coding frame and the systematic coding process itself eased the index frame process as similar mentions could be more easily grouped together.

Table: Coding frame

| Coded matter | Code number | Reason why this piece of text was coded and what kind of information the code contains? | Other (What was gained with this coded information, linkage to other codes) |
|---|---|---|---|
| Job description | 1 | Internal audits are done alongside other duties and assignments. How internal audits were linked with the person`s work and their involvement in this process could be pieced together. | Was not further used in the analysis. Gave knowledge about the background of the interviewee and was used to find causes for deviant case analysis. |
| People participating in the internal audit process and their role. | 2 | Different roles and expertise of people participating in internal audits. Distribution of responsibility in the audit process. | Is linked with the preparation or planning phase when considering who participates in the audit. Was used in the outlining of the audit process. |
| Internal auditor`s attributes | 2a | What kind of attributes makes a good internal auditor? What is required from an internal auditor? | Sub group of the former code! |
| Selection of audit topic | 3 | Selection of audit topic was emphasized in many occasions. What kind of topics should be selected and how the selection is done. | Is linked with planning and preparation for audit |
| On-site activities of the internal audits | 4 | How the on-site activities of the internal audit proceeded or should proceed. Details about the practice. | Was used in the outlining of the audit process. |
| Aim of the internal audit | 5 | Aim of the internal audit? Why internal audits are done, should be done? | This was a direct question from the interview schedule. |
| External audits | 6 | Internal audits were compared with external audits. How the findings of these audits could be compared and better utilised. | Could these two forms of auditing complete each other or should these be considered only separately. |
| Corrective action | 7 | Corrective action is considered part of internal audit as the findings often lead to corrective action. How this phase is handled? | Was used in the outlining of the audit process. Was considered as a weak point of the audit process. |
| Openness | 8 | Matters are brought forth openly in internal audits, not covered up for. Foundation for good cooperation. | Important factor of a functioning internal audit. Is also linked with cooperation. |
| Decision making | 9 | Decisions about the action to internal audit findings. How the decisions are done and on what grounds? Internal audits are a source of information on which decisions can be based on. | Is linked with corrective action and audit findings. |
| Cooperation | 10 | Teamwork at different levels. Within and Between departments, sites and different participants in internal audits. | Important factor of a functioning internal audit. |
| Harmonisation of operations | 11 | Easier to manage operations when they are harmonized. | |
| Distribution of best practices | 11a | Not only focusing on the “negative” in internal audits. Figuring out what works and learning from it. | Utilisation of internal audit. Linked with information flow and part of harmonisation of operations. |
| Varied ways of action | 11b | Different ways to interpret guidance and different ways to execute the operations. | Should these be harmonised or is some variation good. Should guidance be flexible so each department can adapt it how it best suits them or should it be stricter? |
| Distribution of knowledge | 11c | Know-how about processes should be distributed to improve the operations. | Utilisation of internal audits |

| | | | |
|---|---|---|---|
| Follow-up | 12 | How the internal audit findings and corrective actions/improvements are going according to plans? | Was used in the outlining of the audit process. |
| Preparation | 13 | Important part of the audit process. Gathering documents, getting people together. | |
| Maintenance of knowledge | 14 | Keeping up skills and knowledge about the processes, training, lifelong learning. | |
| Internal audit findings | 15 | What kinds of findings are emerged in internal audits? What kinds of things are looked for? Do these tell something about the QMS? | |
| Flow of information, communication | 16 | How information flows within and between departments/sites? How internal audit proceeds and how this is communicated and distributed to others? | Is linked with cooperation, training and decision making. |
| Division of (corrective) actions to minor and major actions | 17 | Actions taken based on the audit findings could be divided into minor and major based on how severe the findings were. Minor findings were found easy to repair with the current systems. Difficulties lay with the major actions required by the more complex and challenging findings. | Is linked with audit findings, corrective action, and flow of information. |
| Development of internal audit | 18 | Internal audit is part of QMS and needs to be developed alongside it. | |
| Effectiveness of operations | 19 | Effectiveness of operations can be evaluated with the help of internal audits | Utilisation of internal audits |
| Measuring instruments | 20 | Indicators about how internal audits have benefited the audited process. Have improvements been made because of internal audits? | |
| Follow-up of audit activities | 21 | What kind of effect the audit has had? Evaluation of the influence of audit and its findings. | |
| Management of internal audits | 22 | Management of time, being on schedule, Effective and clear internal audit, development and improvement of the audit process. | |
| ”the finishing touches” | 23 | Completion of actions to internal audit findings were found challenging. Reasons why some things are hard to follow through? What should be done to fix this? | |
| Training | 24 | Action to internal audit findings. Way to distribute information. | Linked with flow and distribution of information. |
| Development of operations | 25 | Comprehensive development and improvement of operations based on audit findings and activities. | Is linked with corrective actions, change management and improvements as these all aim to utilize the information from internal audits to gain knowledge about own operations and fix/improve them. |
| Change management | 26 | As big improvements are done and systems are developed further, change management is needed to safely and systematically implement change. | Linked to corrective action and development of operations. It is a response to internal audit findings. Is part of the “follow-up actions”. |
| Procedures which guide the operations | 27 | Role of procedures in improving and changing operations and processes. Harmonising procedures may harmonise operations. Should the procedure or operation be changed to improve systems? | Linked with harmonisation and development of operations. |
| Quality systems | 28 | Mentions made about quality systems. What kind of information can be gathered about quality systems with internal audits? | Links together the whole audit process with quality systems. |

| | | | |
|---|---|---|---|
| Amount and extent of internal audits | 29 | The amount, extent and frequency of internal audits done in the site. | Linked with planning of audit, selection of audit topics and preparation. |
| Requirement | 30 | Internal audits considered as a regulatory requirement set by authorities | |
| Quality system audit | 31 | Quality system audits are compared with regular internal audits. | |
| Internal audits directed at QA | 32 | These interviews handled the internal audits done by QA directed at manufacturing. What about the other way around? | Do the same rules apply? |
| Risk analysis | 33 | Risk analysis concerning what topics should be picked and what should be concentrated on in the audits. | Linked with the selection of internal audit topics. |
| Gaining knowledge about own operations | 34 | With internal audits knowledge about own operations can be gathered and used to improve operations, distribute this information and make decisions based on the information. Figuring out strengths and weaknesses. | Linked with development of operations, distribution of information, harmonization, decision making. |

APPENDIX 3

Index frame

Coded pieces of text from raw data were gathered in the index frame with ”copy & paste” method. The indentifying mark and code number was also placed in the index frame to be able to trace back this piece of information. Each coded fragment was placed either directly to a specific category or a sub category which was later organized to be part of a top category. Index frame had own section to make notes and memo which related to the coded text or the category. The index frame also contained places for deviant case and numerical information about the categories.

Index frame was processed with Excel. The next Table shows the outline of the index frame and an example of raw data placed in the index frame.

Table: Index frame with an example

| **Category (Label: description)** | **Sub category (Description and Links to other categories)** | **Text QA (”copy & paste” method from transcripts with codes)** | **Text Manufacturing (”copy & paste” method from transcripts with codes)** | **Notes (Thoughts)** | **Deviant case (Quote)** | **Quantitative information about the category** |
|---|---|---|---|---|---|---|
| Planning and preparation phase of internal audit | Selection of internal audit topic | *“.. based on what kind of problems has occurred in production.”* 2Q3<br>*“Topic from a higher quarter, which is looked through in every department”* 2Q3 | *“Suitable program and selection of topics over the whole field done in cooperation with QA and manufacturing”* 1M3 | | | Sum of similar opinions |
| | Different roles and skills of people participating in the audit process in general | *“They are experts in their own field.”* 1Q2<br>*“Persons in charge and the people with the main responsibilities need to be determined in forehand“* 4Q2 | *“About 5-10 people from different fields participate in the individual internal audit process”* 3M2 | | *“Everybody should work together as a team. In this sense, the roles are not that substantial”* 5Q2 | |
| | Auditor`s role and skills | *“Experience and preparation is important”* 1Q2a | *“Internal auditor needs to have the skill to challenge matters”* 2M2a | | | |
| | Preparation | *“enough time to prepare in forehand”* 2Q13 | *“Familiarization with the topic. Going through SOPs and notifications. Preparing to answer some questions.”* 4M13 | | | |

APPENDIX 4

Excel has a statistical function called CHITEST which calculates the p-value. Null hypothesis is that the results are independent and this can be disregarded if gained result from CHITEST is lower than significance level of 0.05 ($p<0.05$). This indicates that variables are dependent. Chi-square tests were done with Excel. In a 2 X 2 test the degree of freedom is 1. In a 2 X 3 test the degree of freedom is 2. The calculations made on excel take the degree of freedom into account.

The expected values were calculated based on the observed values and how these would be statistically distributed. The total of a row times the total of a column divided by the sum total of the whole table gives the expected value for one cell (e.g. 8x14/19=5.90 for the first cell in CHI-SQUARE TESTS Table 1.).

CHI-SQUARE TESTS

1. Positive and negative opinions about monitoring QMS with internal audits by QA and manufacturing

| Obseved | Positive | Negative | Opinions |
|---|---|---|---|
| QA | 6 | 2 | 8 |
| MA | 8 | 3 | 11 |
| Sum | 14 | 5 | 19 |

| Expected | Positive | Negative | Opinions |
|---|---|---|---|
| QA | 5.90 | 2.11 | 8 |
| MA | 8.11 | 2.90 | 11 |
| Sum | 14 | 5 | 19 |

| | |
|---|---|
| CHITEST (Probability) | 0.912 |

2. Positive and negative opinions about guiding QMS with internal audits by QA and manufacturing

| Observed | Positive | Negative | Opinions |
|---|---|---|---|
| QA | 10 | 2 | 12 |
| MA | 9 | 4 | 13 |
| Sum | 19 | 6 | 26 |

| Expected | Positive | Negative | Opinions |
|---|---|---|---|
| QA | 9.12 | 2.88 | 12 |
| MA | 9.88 | 3.12 | 13 |
| Sum | 19 | 6 | 26 |

CHITEST 0.409

3. Well functioning and Challenging aspects of internal audit process

| Observed | Well functioning | Challenges | Sum |
|---|---|---|---|
| QA | 6 | 5 | 11 |
| MA | 6 | 4 | 10 |
| Sum | 12 | 9 | 21 |

| Expected | Well functioning | Challenges | Sum |
|---|---|---|---|
| QA | 6.29 | 4.71 | 11 |
| MA | 5.71 | 4.29 | 10 |
| Sum | 12 | 9 | 21 |

CHITEST 0.801

| Observed | QA | MA | Sum |
|---|---|---|---|
| Well | 6 | 6 | 12 |
| Challenging | 5 | 4 | 9 |
| Sum | 11 | 10 | 21 |

| Expected | QA | MA | Sum |
|---|---|---|---|
| Well | 6.29 | 5.71 | 12 |
| Challenging | 4.71 | 4.29 | 9 |
| Sum | 11 | 10 | 21 |

CHITEST 0.801

Well functioning

| Observed | QA | MA | Sum |
|---|---|---|---|
| Teamwork | 4 | 3 | 7 |
| Preparation | 1 | 1 | 2 |
| On-site activities | 1 | 2 | 3 |
| Sum | 6 | 6 | 12 |

| Expected | QA | MA | Sum |
|---|---|---|---|
| Teamwork | 3.50 | 3.50 | 7 |
| Preparation | 1.00 | 1.00 | 2 |
| On-site activities | 1.50 | 1.50 | 3 |
| Sum | 6 | 6 | 12 |

CHITEST 0.788

Challenging

| Observed | QA | MA | Sum |
|---|---|---|---|
| Corrective actions | 4 | 1 | 5 |
| Completion | 1 | 1 | 2 |
| On-site | 0 | 2 | 2 |
| Sum | 5 | 4 | 9 |

| Expected | QA | MA | Sum |
|---|---|---|---|
| Corrective actions | 2.78 | 2.22 | 5 |
| Completion | 1.11 | 0.89 | 2 |
| On-site | 1.11 | 0.89 | 2 |
| Sum | 5 | 4 | 9 |

CHITEST 0.155